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(54) Title: HETEROCYCLIC DERIVATIVES AS GPCR RECEPTOR AGONISTS

(57) Abstract: Compounds of Formula (I), $R^1$-A-V-B-$R^2$; or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

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TITLE OF THE INVENTION

# HETEROCYCLIC DERIVATIVES AS GPCR RECEPTOR AGONISTS

## BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to agonists of GPR116 that are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)$^2$), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) which is characterized by hypertension and its associated pathologies including atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with decreased insulin sensitivity which can lead to abnormal blood sugar levels when challenged. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR116 is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, US 6,468,756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and ANN95196 (mouse)).

In humans, GPR116 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR116 receptor indicates its potential utility as a target for the treatment of obesity and diabetes.

Williams J.P., Combinatorial Chemistry & High Throughput Screening, 2000, 3, 43-50 discloses the compounds 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine and 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester, synthesised as part of a compound library designed to identify dopamine $D_4$ ligands.

The compounds 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine and 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chem Div) and 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chembridge) are / were commercially available. No pharmaceutical utility has been suggested for these compounds.

The present invention relates to agonists of GPR116 which are useful as peripheral regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

## SUMMARY OF THE INVENTION

Compounds of formula (I):

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. in the prophylactic or therapeutic treatment of obesity, and for the treatment of diabetes.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S, optionally substituted by $C_{1-4}$ alkyl;

A is -CH=CH- or $(CH_2)_n$;

B is -CH=CH- or $(CH_2)_n$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$, C(O) or $C(O)NR^{12}$;

n is independently 0, 1, 2 or 3;

m is independently 0, 1 or 2;

$R^1$ is 3- or 4-pyridyl, 4- or 5-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

$R^2$ is 4- to 7-membered cycloalkyl substituted by $R^3$, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$, $P(O)(OR^{11})_2$ or a 5- or 6-membered nitrogen containing heteroaryl group;

$R^3$ is $C_{3-8}$ alkyl, $C_{3-8}$ alkenyl or $C_{3-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be optionally substituted with one or

more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^5$ is hydrogen, $C(O)R^7$, $S(O)_2R^8$, $C_{3-7}$ cycloalkyl or $C_{1-4}$ alkyl optionally substituted by $OR^6$, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-2}$ alkyl, $C_{1-2}$ fluoroalkyl, $OR^6$, CN, $N(R^6)_2$ and $NO_2$;

$R^6$ are independently hydrogen, $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^7$ is hydrogen, $C_{1-4}$ alkyl, $OR^6$, $N(R^6)_2$, aryl or heteroaryl;

$R^8$ is $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, aryl or heteroaryl;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl;

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl;

$R^{11}$ is phenyl; and

$R^{12}$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-7}$ cycloalkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester;

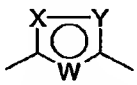
c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600, especially less than 500.

In the compounds of formula (I) V is preferably a 5-membered heteroaryl ring containing up to three heteroatoms selected from O, N and S of the formula:




wherein W, X and Y represent the positions of the heteroatom(s) or otherwise represent CH.

Particular heterocyclic rings which V may represent include oxadiazole, oxazole, isoxazole, thiadiazole, thiazole and pyrazole.

Preferably two of W, X and Y are N, and the other is O.

W is preferably N.

Preferably the n groups of A and B do not both represent 0.

In A, n is preferably 0, 1 or 2, more preferably 0.

In B, n is preferably 2 or 3, more preferably 2.

When one of the $CH_2$ groups in B is replaced, it is preferably replaced by O, $NR^5$, $S(O)_m$ or C(O); more preferably it is replaced by O or $NR^5$.

$R^1$ is preferably 4-pyridyl optionally substituted by 1 or 2 halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)$, 4- to 7-membered heterocyclyl or 5- or 6-membered heteroaryl groups; more preferably 4-pyridyl optionally substituted by halo, $C_{1-4}$ alkyl $C_{1-4}$ alkoxy or CN; even more preferably 4-pyridyl, optionally substituted by halo, $C_{1-4}$ alkyl or CN; and especially 4-pyridyl, optionally substituted by CN.

When $R^2$ is a 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms it is preferably substituted, the substitution is preferably on the nitrogen atom.

$R^2$ is preferably a 4- to 7-membered cycloalkyl substituted by $R^3$ or $C(O)OR^3$, especially $R^3$, or 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by $C(O)OR^4$ or a 6-membered nitrogen containing heteroaryl group, more preferably a 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by $C(O)OR^4$.

A particularly preferred $R^2$ group is piperidinyl, especially 4-piperidinyl, which is substituted on the nitrogen atom by $C(O)OR^4$.

$R^3$ is preferably $C_{3-8}$ alkyl which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, more preferably $R^3$ is $C_{3-8}$ alkyl.

$R^4$ is preferably $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, 5- to 6-membered heteroaryl containing one or two nitrogen atoms, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl or $C_{1-4}$ alkylaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$ and $CO_2C_{1-4}$ alkyl.

More preferably $R^4$ is $C_{3-6}$ alkyl optionally substituted with up to 5 fluoro or chloro atoms, e.g. 3 fluoro or chloro atoms, and which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl.

$R^5$ is preferably hydrogen or $C_{1-4}$ alkyl, more preferably $C_{1-4}$ alkyl.

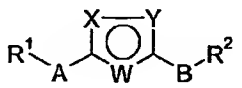
$R^6$ is preferably hydrogen, $C_{1-4}$ alkyl or $C_{3-7}$ cycloalkyl, more preferably $C_{1-4}$ alkyl.

$R^7$ is preferably hydrogen or $C_{1-4}$ alkyl.

$R^8$ is preferably $C_{1-4}$ alkyl or $C_{1-4}$ fluoroalkyl.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups. The preferences listed above also apply, where applicable, to the compounds of formula (Ia) to (Ie) below.

A particular group of compounds which may be mentioned are the compounds of formula (Ia) and pharmaceutically acceptable salts thereof:



(Ia)

where two of W, X and Y are N, and the other is O;

A is -CH=CH- or $(CH_2)_n$;

B is -CH=CH- or $(CH_2)_n$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$, C(O) or $C(O)NR^{12}$;

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

$R^1$ is 3- or 4-pyridyl, 4-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{3-7}$ cycloalkyl, $OR^{6a}$, CN, $NO_2$, $S(O)_mR^{6b}$, $N(R^6)_2$, $CON(R^{6b})_2$ or a 5- or 6-membered heteroaryl group;

$R^2$ is 4- to 7-membered cycloalkyl substituted by $R^3$, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms, which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$, $P(O)(OR^{11})_2$ or a 5- or 6-membered nitrogen containing heteroaryl group;

$R^3$ is $C_{3-8}$ alkyl, $C_{3-8}$ alkenyl or $C_{3-8}$ alkynyl, any of which may be optionally substituted with up to 5 chloro or fluoro atoms, and which may also contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, aryl or $C_{1-4}$ alkylaryl, wherein the cycloalkyl groups may be optionally substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl, and the aryl groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^{6a}$, $COOR^{6a}$, CN, $N(R^{6b})_2$ and $NO_2$;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 chloro or fluoro atoms, and which may also contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, aryl or $C_{1-4}$ alkylaryl, wherein the cycloalkyl groups may be optionally substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl, and the aryl groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^{6a}$, $COOR^{6a}$, CN, $N(R^{6b})_2$ and $NO_2$;

$R^5$ are independently hydrogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl;

$R^{6a}$ are independently hydrogen, $C_{1-4}$ alkyl or $C_{1-4}$ fluoroalkyl;

$R^{6b}$ are independently hydrogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl;

$R^{11}$ is phenyl; and

$R^{12}$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-7}$ cycloalkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester;

c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

A further group of compounds which may be mentioned are the compounds of formula (Ib) and pharmaceutically acceptable salts thereof:

$$R^1\text{-A-V-B-}R^2$$

(Ib)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S;

A is $(CH_2)_n$;

B is $(CH_2)_n$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

$R^1$ is 3- or 4-pyridyl or 4- or 5-pyrimidinyl, any of which may be optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

$R^2$ is 4- to 7-membered cycloalkyl substituted by $R^3$, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms, which are unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$ or $S(O)_2R^3$;

$R^3$ is $C_{3-7}$ alkyl, $C_{3-7}$ alkenyl or $C_{3-7}$ alkynyl which may contain a $CH_2$ group that may be replaced by O, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $N(R^6)_2$ and $NO_2$;

$R^4$ is $C_{2-7}$ alkyl, $C_{2-7}$ alkenyl or $C_{2-7}$ alkynyl which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $N(R^6)_2$ and $NO_2$;

$R^5$ is hydrogen, $C(O)R^7$, $S(O)_2R^8$ or $C_{1-4}$ alkyl optionally substituted by $OR^6$, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-2}$ alkyl, $C_{1-2}$ fluoroalkyl, $OR^6$, CN, $N(R^6)_2$ and $NO_2$;

$R^6$ are independently hydrogen, or $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl group or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^7$ is hydrogen, $C_{1-4}$ alkyl, $OR^6$, $N(R^6)_2$ aryl or heteroaryl;

$R^8$ is $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, aryl or heteroaryl;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl; and

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

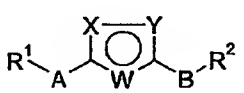
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester;

c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

A further specific group of compounds of the invention which may be mentioned are those of formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

where two of W, X and Y are N, and the other is O;

A is $(CH_2)_n$;

B is $(CH_2)_m$, where one of the $CH_2$ groups may be replaced by O, $NR^6$, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

$R^1$ is 3- or 4-pyridyl or 4-pyrimidinyl any of which may be optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{3-7}$ cycloalkyl, $OR^5$, CN, $NO_2$, $N(R^6)_2$, $CON(R^6)_2$ or a 5- or 6-membered heteroaryl group;

$R^2$ is 4- to 7-membered cycloalkyl substituted by $R^3$, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms, which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$ or $S(O)_2R^3$;

$R^3$ is $C_{3-7}$ alkyl, $C_{3-7}$ alkenyl or $C_{3-7}$ alkynyl any of which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl or $C_{1-4}$ alkylaryl, wherein the aryl groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^5$, CN, $N(R^6)_2$ and $NO_2$;

$R^4$ is $C_{2-7}$ alkyl, $C_{2-7}$ alkenyl or $C_{2-7}$ alkynyl any of which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl or $C_{1-4}$ alkylaryl, wherein the aryl groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^5$, CN, $N(R^6)_2$ and $NO_2$;

$R^5$ are independently hydrogen, $C_{1-4}$ alkyl or $C_{1-4}$ fluoroalkyl; and

$R^6$ are independently hydrogen and $C_{1-4}$ alkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

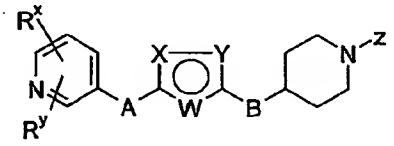
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester;

c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

A preferred group of compounds of the invention are the compounds of formula (Id), and pharmaceutically acceptable salts thereof:




(Id)

where two of W, X and Y are N, and the other is O;

A is -CH=CH- or $(CH_2)_n$;

B is -CH=CH- or $(CH_2)_m$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3, provided that not both n are 0;

m is independently 0, 1 or 2;

$R^x$ and $R^y$ are independently selected from hydrogen, halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$,

$NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group and a 5- or 6-membered heteroaryl group;

Z is $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$ or a 5- or 6-membered nitrogen containing heteroaryl group;

$R^3$ is $C_{3-8}$ alkyl, $C_{3-8}$ alkenyl or $C_{3-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

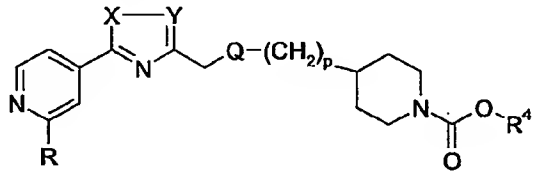
$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^6$ are independently hydrogen, or $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl; and

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl.

A further preferred group of compounds of the invention are the compounds of formula (Ie), and pharmaceutically acceptable salts thereof:



(Ie)

wherein one of X and Y is N, and the other is O;

Q is O, $NR^5$ or $CH_2$;

R is hydrogen, halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^5$ is $C_{1-4}$ alkyl;

$R^6$ are independently hydrogen, or $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl;

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl; and

p is 0 or 1.

In the compounds of formula (Ie) R is preferably hydrogen, halo, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy or CN.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

Particular compounds which may be mentioned are:

4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester,

4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester,

4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester,

4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester,

4-[Ethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester,

4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid cyclopentyl ester, and

4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester,

and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term "fluoroalkyl" includes alkyl groups substituted by one or more fluorine atoms, e.g. $CH_2F$, $CHF_2$ and $CF_3$.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes monocyclic saturated carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "halo" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" includes phenyl and naphthyl, in particular phenyl.

Unless otherwise indicated the term "heterocyclyl" and "heterocyclic ring" includes 4- to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of

heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Examples of heterocyclic rings that $R^2$ may represent include azetidine, pyrrolidine, piperidine and piperazine. $R^2$ heterocyclyl groups may also contain additional heteroatoms, e.g. morpholine.

Unless otherwise stated, the term "heteroaryl" includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline and purine.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

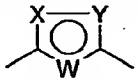
The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from

pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N',N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

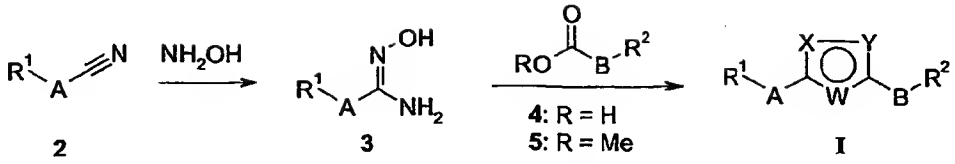
The compounds of formula (I) can be prepared as described below, in which, for illustrative purposes, -V- is shown as a group of the formula:




and $R^1$, $R^2$, $R^3$, $R^4$, A, B, W, X and Y are as defined above.

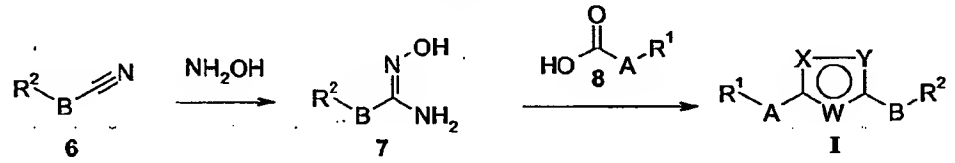
The compounds of formula (I), in which X = N, Y = O and W = N, may be prepared according to the method illustrated in Scheme 1. The nitriles of formula **2** are either commercially available or can be synthesised using known techniques. Compounds of formula **2** are treated with hydroxylamine in a suitable solvent, such as ethanol-water, at elevated temperature, to afford amidoximes of formula **3** (synthesis of amidoximes is further described by A. R. Martin et al, J. Med. Chem., 2001, 44, 1560). Compounds of formula **3** are subsequently condensed with acids of formula **4**, which are themselves either commercially available or can be readily synthesised using known techniques. The condensation firstly entails activation of compounds of formula **4** by, for example, formation of the mixed anhydride, in which the acid is treated with a chloroformate, such as isobutylchloroformate, in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as THF or toluene, followed by addition of compounds of formula **3**. Alternatively, compounds of formula **4** may be activated by conversion to the acid halide, generated by treatment of the acid with, for example, oxalyl chloride in a suitable solvent, such as $CH_2Cl_2$-DMF. The intermediates arising from the condensation of amidoximes of formula **3** and acids of formula **4** are dissolved in an appropriate solvent, such as toluene or xylene, and heated under reflux, with concomitant removal of water by Dean-Stark apparatus or by molecular sieves, to form oxadiazoles of formula (I). Alternatively, amidoximes of formula **3** can firstly be treated with a suitable base, for example sodium hydride, in an appropriate solvent, such as THF, and subsequently esters of formula **5**. Heating of this mixture also generates oxadiazoles of formula (I) (this process is further illustrated by R. H. Mach et al, Bioorg. Med. Chem., 2001, 9, 3113).

**Scheme 1**



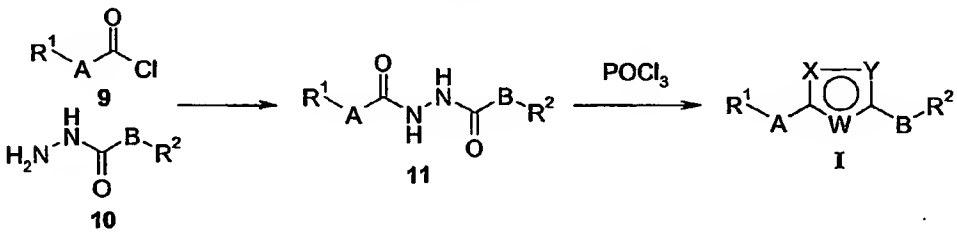

Compounds of formula (I) in which X = O, Y = N and W = N may be prepared according to the method outlined in Scheme 2. The nitriles of formula **6** are either commercially available or can be synthesised using known techniques. These are converted to the corresponding amidoximes of formula **7**, as described above, and subsequently condensed with acids of formula **8**, which are commercially available or can readily be synthesised by those skilled in the art. This condensation is performed in a fashion analogous to that described in Scheme 1, to afford the corresponding oxadiazoles of formula (I).

**Scheme 2**



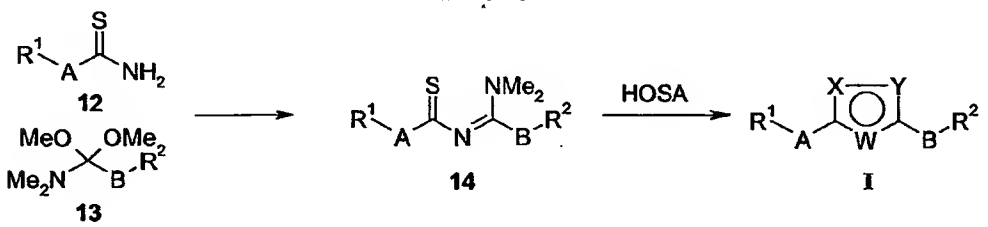

Compounds of formula (I) in which X = N, Y = N and W = O can be synthesised as outlined in Scheme 3. The acyl chlorides of formula **9** are either commercially available or may be synthesised using known methods. The acid hydrazides of formula **10** can be readily obtained by, for example, treating an ethanolic solution of the corresponding ester with hydrazine (for further details see K. M. Kahn et al, Bioorg. Med. Chem., 2003, 11, 1381). Treating the acyl chlorides of formula **9** with the acid hydrazides of formula **10** in a suitable solvent, such as pyridine, affords compounds of formula **11** (further illustrated by V. N. Kerr et al, J. Am. Chem. Soc., 1960, 82, 186), which are then converted by $POCl_3$ at elevated temperature to compounds of formula (I) (this process is further described by S-A. Chen et al, J. Am. Chem. Soc., 2001, 123, 2296). Similarly, compounds of formula (I) where X = Y = W = N can be prepared via the condensation of the amidrazone analogue of **10** with the appropriate activated carboxylic acid derivative, such as **9**. The reactive groups in this reaction may be exchanged, i.e., an amidrazone of formula $R^1$–A–C(=NH)$NHNH_2$ can form a compound of formula (I) by condensation with an activated carboxylic acid derivative
LG–C(=O)–B–$R^2$ where LG is halogen or oxycarbonyl (P. H. Olesen et al., J. Med. Chem., 2003, 46, 3333–3341).

**Scheme 3**



Compounds of formula (I) where X = N, Y = N, and W = S can also be prepared from compounds of formula **11** by heating with Lawesson's reagent in a suitable solvent, such as toluene or acetonitrile (D. Alker et al., J. Med. Chem., 1989, 32, 2381-2388). Compounds of formula (I) where X = S, Y = N and W = N can be formed from compounds of formula **12** (Scheme 4) which are commercially available, or can be readily synthesised from the corresponding carbonyl compound and Lawesson's reagent under standard conditions. Treating a compound of formula **12** with a compound of formula **13** in a suitable solvent such as dichloromethane at about 20°C gives compounds of formula **14**. Compounds of formula **13** can be obtained by treating the corresponding dimethylamide with Meerwein's reagent (for details see M. Brown US 3,092,637). Compounds of formula **14** are then cyclised using hydroxylamine-*O*-sulfonic acid in the presence of a base, such as pyridine, in a suitable solvent such as methanol (for further details, see A. MacLeod et al, J. Med. Chem., 1990, 33, 2052).

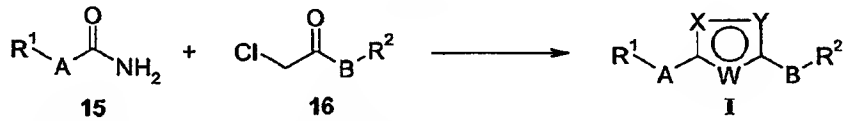
**Scheme 4**




The regioisomeric derivatives of formula (I), where X = N, Y = S and W = N, can be formed in a similar manner by reversing the functionality of the reactants so the $R^1$ fragment contains the acetal moiety and the $R^2$ fragment contains the thiocarbonyl.

Compounds of formula (I) where W = O, X = N and Y = CH can be formed from compounds of formula **15** (Scheme 5). Compounds of formula **15** are commercially available or synthesised using known techniques. Chlorides of formula **16** are commercially available, or can readily be formed by chlorinating the corresponding ketone using standard conditions, for example, bubbling chlorine gas through a methanol solution of the ketone (for further details see R. Gallucci & R. Going, J. Org. Chem., 1981, 46, 2532). Mixing a compound of formula **15** with a chloride of formula **16** in a suitable solvent, such as toluene, with heating, for instance at about 100°C gives compounds of formula (I) (for further information, see A. Hassner et al, Tetrahedron, 1989, 45, 6249). Compounds of formula (I) where W = O, X = CH and Y = N can be formed is a similar fashion by reversing the functionality of the reactants so the $R^1$ fragment contains the haloketone moiety and the $R^2$ fragment contains the $C(O)NH_2$.

**Scheme 5**

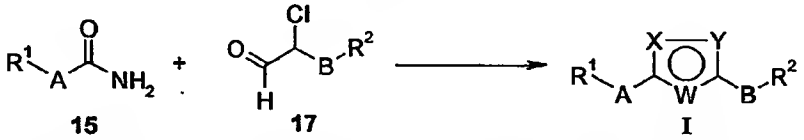



Alternatively, compounds of formula (I) where X = S, W = N and Y = CH can also be formed from compounds of formula **16**. Heating an compound of formula **15** with phosphorus pentasulfide, followed by the addition of a compound of formula **16** followed by further heating gives compounds of formula (I) (for further details, see R. Kurkjy & E. Brown, J. Am. Chem. Soc., 1952, 74, 5778). The regioisomeric compounds where X = CH, W = N and Y = S can be

formed is a similar fashion by reversing the functionality of the reactants, so the $R^1$ fragment contains the haloketone moiety and the $R^2$ fragment contains the $C(O)NH_2$.

Compounds of formula I where W = N, X = O and Y = CH can be formed from compounds of formula **15** and formula **17** (Scheme 6) under similar conditions to those outlined for Scheme 5. Compounds of formula I where W = S, X = N and Y = CH can also be formed from compounds of formula **15** and formula **17** using the conditions involving phosphorus pentasulfide described above.

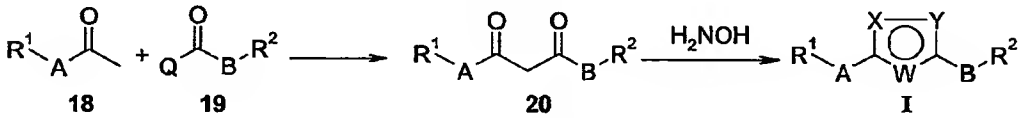
**Scheme 6**



**15** **17** **I**

Compounds of formula (I) where X = O, Y = N and W = CH, and where X = N, Y = O and W = CH and can be formed from compounds of formula **20** (Scheme 7). Acylation of compounds of formula **18** with a compound of formula **19**, where Q is alkoxide or chloride, can occur under standard conditions, for example, deprotonation of ketone **18** with a suitable base, such as lithium diisopropylamide or potassium ethoxide, in a suitable solvent, such as tetrahydrofuran, generally at low temperature. Treatment of compounds of formula **20** with hydroxylamine, in a suitable solvent, such as ethanol, at elevated temperature, for example 75°C, yields compounds of formula (I) as a mixture of both regioisomers of the isoxazole. Using standard separation techniques, such as chromatography on silica gel, the individual isomers can be isolated (for further details, see M. Rowley et al, J. Med. Chem., 1997, 40, 2374).

**Scheme 7**



**18** **19** **20** **I**

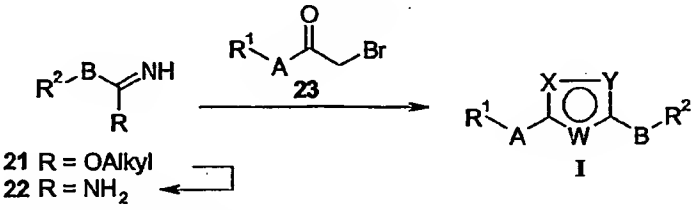
Compounds of formula (I) where X = S, Y = N and W = CH can be formed by hydrogenation of a compound of formula (I) where X = O, Y = N and W = CH, with platinum oxide in a suitable solvent such as ethanol, followed by heating with phosphorus pentasulfide to give compounds of formula (I) where X = S, Y = N and W = CH (for further details, see G. Wiegand et al, J. Med. Chem., 1971, 14, 1015). For details of the synthesis of the regioisomer where X = N, Y = S and W = CH also see G. Wiegand *ibid*).

Compounds of formula (I) where X = N, Y = N and W = CH can be formed from compounds of formula **20**. Treatment of compounds of formula **20** with hydrazine in a suitable solvent, such as methanol, would give rise to compounds of formula (I) where X = N, Y = N and W = CH (this process is further illustrated by R. Baker et al, J. Med. Chem., 1997, 40, 2374).

Compounds of formula (I) in which X = CH, Y = N and W = N can be synthesised as described in Scheme 8. Bromides of formula **23** are either commercially available or may be synthesised from the corresponding ketone by, for example, treating an aqueous solution of the ketone with $Br_2$ and HBr (as described by J. Y. Becker et al, Tetrahedron Lett., 2001, 42, 1571). The amidines of formula **22** may be synthesised by known methods, for example by treatment of the corresponding alkyl imidates of formula **21** with ammonia in a suitable solvent, such as

ethanol (as detailed by D. A. Pearson et al, J. Med. Chem., 1996, 39, 1372). The imidates of formula **21** may in turn be generated by, for example, treatment of the corresponding nitrile with HCl in a suitable solvent, such as methanol (for further details see J. P. Lokensgard et al, J. Org. Chem., 1985, 50, 5609). Reaction of amidines of formula **22** with bromides of formula **23** in a suitable solvent, such as DMF, affords compounds of formula (I) (illustrated by N. J. Liverton et al, J. Med. Chem., 1999, 42, 2180).

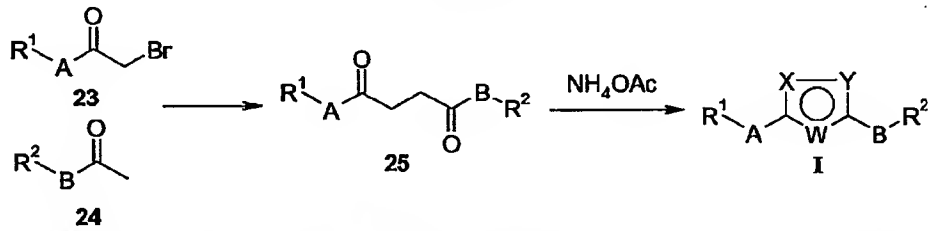
**Scheme 8**




The regioisomeric compounds where X = N, Y = CH and W = N can be formed in a similar fashion by reversing the functionality of the reactants, so the $R^1$ fragment contains the amidine moiety and the $R^2$ fragment contains the bromide.

Compounds of formula (I) in which X = CH, Y = CH and W = N can be synthesised as illustrated in Scheme 9. Diketones of formula **25** are readily accessible by, for example, the condensation of ketones of formula **24**, which are commercially available or are readily synthesised using known techniques, with bromides of formula **23** in a suitable solvent, such as benzene using an appropriate catalyst. Illustrative examples are described by O. G. Kulinkovich et al, Synthesis, 2000, 9, 1259. Using a Paal-Knorr reaction, diketones of formula **25** may be treated with, for example, ammonium carbonate in a suitable solvent, such as ethanol at elevated temperature (for further details see R. A. Jones et al, Tetrahedron, 1996, 52, 8707) to afford compounds of formula (I).

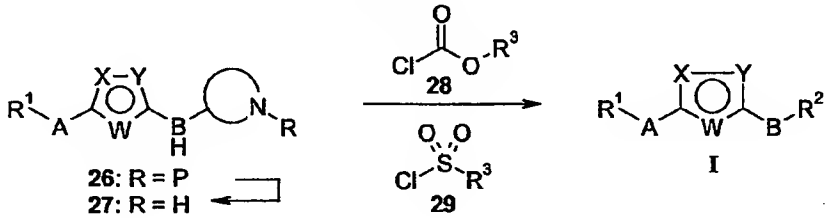
**Scheme 9**




Compounds of formula (I) in which $R^2$ contains either a carbamate or a sulfonamide group may be synthesised as described in Scheme 10. Compounds of formula **26**, in which P represents a suitable protecting group, for example *tert*-butoxycarbonyl (Boc), may be synthesised as outlined in Schemes 1-9 above. The protecting group is firstly removed under suitable conditions to afford compounds of formula **27**. In the case of the Boc group this can be achieved by treatment of compounds of formula **26** with a suitable acid, such as trifluoroacetic acid, in an appropriate solvent, such as $CH_2Cl_2$. Treatment of compounds of formula **27** with chloroformates of formula **28**, which are generally commercially available or can be readily synthesised, in a suitable solvent, such as $CH_2Cl_2$, in the presence of a suitable base, such as triethylamine, affords compounds of formula (I). Similarly, compounds of formula **27** may be reacted with sulfonyl chlorides of formula **29**, which are generally commercially available or

can readily be synthesised, in a suitable solvent, such as $CH_2Cl_2$, in the presence of a suitable base, such as triethylamine, to afford compounds of formula (I). Compounds of formula (I) in which $R^2$ contains a urea moiety may be prepared by reacting a compound of formula 13 with an isocyanate of formula $O=C=N-R^4$. Furthermore, compounds of formula (I) in which $R^2$ is 4–7-membered heterocyclyl substituted with a heteroaryl group may be prepared by reacting the amine **27** with the appropriate heteroaryl chloride or bromide under Pd(0) catalysis in the presence of a suitable ligand and base (Urgaonkar, S.; Hu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416–8423).

**Scheme 10**




Compounds of formula (I) in which $R^2$ contains an amide group may be synthesised from compounds of formula **27** and a suitable acid ($R^3COOH$), or activated derivative thereof, in an amide bond forming reaction.

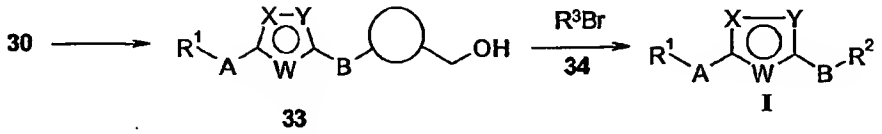
Compounds of formula (I) where $R^2$ contains an ester moiety may be synthesised as illustrated in Scheme 11. Compounds of formula **30** in which R is an alkyl group, for example a methyl group, may be synthesised using procedures described in Schemes 1-9. The alkyl group is firstly removed under appropriate conditions to afford compounds of formula **31**. For example, when R = Me compounds of formula **30** may be hydrolysed in the presence of a suitable alkali, for example LiOH, in a suitable solvent, such as water-methanol. The acids of formula **31** are then condensed with alcohols of formula **32**, which are commercially available or can be synthesised using known techniques. The condensation may be achieved by, for example, treating compounds of formula **31** with alcohols of formula **32** in the presence of thionyl chloride, giving rise to compounds of formula (I).

**Scheme 11**


Compounds of formula (I) where $R^3$ contains an ether group may also be synthesised from compounds of formula **30** as illustrated in Scheme 12. Compounds of formula **30** may be converted to the corresponding alcohol **33** by the action of a suitable reducing agent, for example diisobutylaluminium hydride, in a suitable solvent, such as $CH_2Cl_2$, and can then be treated firstly with a suitable base, such as sodium hydride, in a suitable solvent, such as THF,

followed by an appropriate alkylating agent, such as an alkyl halide of formula 34 to afford compounds of formula (I).

**Scheme 12**




Compounds of formula (I) where B contains a $NR^5$ group where $R^5$ is hydrogen can be further transformed into compounds of formula (I) where $R^5$ is $C(O)R^7$, $S(O)_2R^8$, or an optionally substituted $C_{1-4}$ alkyl group using standard techniques known to those with skill in the art for acylation, sulfonylation and reductive amination, respectively.

Compounds of the formula (I) where $R^1$ is pyridyl optionally substituted with CN can be prepared from the corresponding unsubstituted pyridine by the Reissert reaction (Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375–1377). Similar reactions can be used to prepare the compounds where $R^1$ is pyridyl optionally substituted with halogen (Walters, M. A.; Shay, J. J. *Tetrahedron Lett.* **1995**, *36*, 7575–7578). The compounds where $R^1$ is pyridyl optionally substituted with halogen can be transformed into the corresponding compounds where $R^1$ is pyridyl optionally substituted with $C_{1-4}$ alkyl by transition metal-catalysed cross-coupling reactions (Fürstner, A., et al. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863).

Other compounds of formula (I) may be prepared by methods analogous to those described above or by methods known *per se*.

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

As indicated above the compounds of formula (I) are useful as GPR116 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of formula (I), including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of

formula (I), including the compounds of provisos c) to e), in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPR116, as a regulators of satiety, e.g. resulting in the prophylactic or therapeutic treatment of obesity, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents,

preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose

suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I), including the compounds of provisos a) to e), may be used in the treatment of diseases or conditions in which GPR116 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which GPR116 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, cardiovascular complications and dyslipidaemia). And the treatment of patients who have an abnormal sensitivity to ingested fats leading to functional dyspepsia

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I), including the compounds of provisos a) to e), or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I), including the compounds of provisos a) to e), may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, mixed PPAR-α/γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-1 antagonists and CB-1 antagonists (or inverse agonists), amylin antagonists, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

Combination therapy comprising the administration of a GPR116 agonist and at least one other antiobesity agent represents a further aspect of the invention.

The present invention also provides a method for the treatment of obesity in a mammal, such as a human, which method comprises administering an effective amount of a GPR116 agonist and another antiobesity agent, to a mammal in need thereof.

The invention also provides the use of a GPR116 agonist and another antiobesity agent for the treatment of obesity.

The invention also provides the use of a GPR116 agonist in the manufacture of a medicament for use in combination with another antiobesity agent, for the treatment of obesity.

The GPR116 agonist and the other antiobesity agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the GPR116 agonist and the other antiobesity agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the GPR116 agonist and the other antiobesity agent(s) allow it, coadministration of the two agents may be preferred.

The invention also provides the use of a GPR116 agonist and another antiobesity agent in the manufacture of a medicament for the treatment of obesity.

The invention also provides a pharmaceutical composition comprising a GPR116 agonist and another antiobesity agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

GPR116 agonists which may be used in the combination therapies according to this aspect of the invention include those compounds described herein and also those disclosed in WO04/065380 and WO04/076413.

GPR116 agonists are of particular use in combination with centrally acting antobesity agents as such combinations may avoid the risk of adverse side effects which may be encountered if two centrally acting antiobesity agents are administered in combination.

The other antiobesity agent for use in the combination therapies according to this aspect of the invention is preferably a CB-1 modulator, e.g. a CB-1 antagonist or inverse agonist. Examples of CB-1 modulators include SR141716 (rimonabant) and SLV-319 ((4*S*)-(-)-3-(4-chlorophenyl)-*N*-methyl-*N*-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide); as well as those compounds disclosed in EP576357, EP656354, WO 03/018060, WO 03/020217, WO 03/020314, WO 03/026647, WO 03/026648, WO 03/027076, WO 03/040105, WO 03/051850, WO 03/051851, WO 03/053431, WO 03/063781, WO 03/075660, WO 03/077847, WO 03/078413, WO 03/082190, WO 03/082191, WO 03/082833, WO 03/084930, WO 03/084943, WO 03/086288, WO 03/087037, WO 03/088968, WO 04/012671, WO 04/013120, WO 04/026301, WO 04/029204, WO 04/034968, WO 04/035566, WO 04/037823 WO 04/052864, WO 04/058145, WO 04/058255, WO 04/060870, WO 04/060888, WO 04/069837, WO 04/069837, WO 04/072076, WO 04/072077, WO 04/078261 and WO 04/108728, and the references disclosed therein.

Other diseases or conditions in which GPR116 has been suggested to play a role include those described in WO 00/50562 and US 6,468,756, for example cardiovascular disorders, hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer's disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

## EXAMPLES

### Materials and methods

Column chromatography was carried out on $SiO_2$ (40–63 mesh) unless specified otherwise.

LCMS data were obtained as follows: Atlantis 3μ $C_{18}$ column (2.1 × 30.0mm, flow rate = 0.85ml/min) eluting with a $H_2O$–MeCN solution containing 0.1% $HCO_2H$ over 6min with UV detection at 220nm. Gradient information: 0.0–0.3min 100% $H_2O$; 0.3–4.25 min: Ramp to 10% $H_2O$–90% $CH_3CN$; 4.25min–4.4min: Ramp to 100% $CH_3CN$; 4.4-4.9min: Hold at 100% MeCN;

4.9–6.0min: Return to 100% $H_2O$. The mass spectra were obtained using an electrospray ionisation source in either the positive ($ES^+$) ion or negative ion ($ES^-$) mode. Atmospheric Pressure Chemical Ionisation (APCI) spectra were obtained on a FinniganMat SSQ 7000C instrument.

$^1H$ nmr spectra were recorded on a Varian Mercury 400 spectrometer, operating at 400 MHz. Chemical shifts are reported as ppm relative to tetramethylsilane ($\delta$=0).

HPLC was performed using a Phenomenex™ 10μ$C_{18}$ column (210 × 21mm) eluting with a $H_2O$-$CH_3CN$ solution at 20ml/min, with UV detection at 220nm. Typical gradient: 0-0.5min, 10% $CH_3CN$-90%$H_2O$; 0.5min-10min, ramp to 90% $CH_3CN$-10% $H_2O$ and hold at 90%$CH_3CN$-10%$H_2O$ for 5min; 15min-16min, return to 10% $CH_3CN$-90% $H_2O$.

The syntheses of the following compounds have been reported previously:

3-(2-Cyanopyridin-4-yl)propyl acetate: P. L. Ornstein et al., J. Med. Chem., 1991, 34, 90–97;

(*N*-Hydroxycarbamimidoylmethyl)carbamic acid *tert*-butyl ester: WO03/082861;

*N*-Hydroxyisonicotinamidine and *N*-hydroxynicotinamidine: A. R. Martin et al, J. Med. Chem., 2001, 44, 1560-1563;

*N*-Hydroxy-2-pyridin-3-ylacetamidine and *N*-hydroxy-2-pyridin-4-ylacetamidine: WO 01/047901;

4-Mercaptopiperidine-1-carboxylic acid *tert*-butyl ester: US Patent 5,317,025;

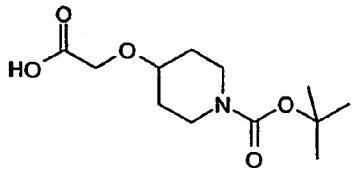
4-Pentylcyclohexanecarbonitrile: J. C. Liang and J. O. Cross, Mol. Cryst. Liq. Cryst., 1986, 133, 235-244;

3-Pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester: EP647635;

4-(3-Bromo-2-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester: WO04/013137.

Abbreviations and acronyms: Ac: Acetyl; Boc: *tert*-Butoxycarbonyl; *t*-Bu: *tert*-Butyl; CDI: 1,1'-Carbonyldiimidazole; dba: dibenzylideneacetone; DMF: *N*,*N*-Dimethylformamide; Et: Ethyl; HPLC: High performance liquid chromatography; IH: Isohexane; LDA: Lithium diisopropylamide; *m*CPBA: 3-Chloroperoxybenzoic acid; Me: Methyl; PDC: Pyridinium dichromate; RP-HPLC: Reverse phase high performance liquid chromatography; RT: Retention time; rt: Room temperature; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran; TMS: Trimethylsilyl.

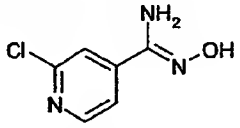
**Preparation 1**: 4-Carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester




Sodium hydride (596mg of a 60% dispersion in oil, 14.9mmol) was added portionwise to a stirred solution of *tert*-butyl-4-hydroxypiperidine-1-carboxylate (1.0g, 5mmol) in anhydrous THF (20ml) at rt. After 15min, bromoacetic acid (1.38g, 9.94mmol) was introduced and stirring continued for 5h. Additional bromoacetic acid (5mmol) and sodium hydride (5mmol) were added and stirring continued for 24h. The reaction was quenched with water (2ml) and diluted with EtOAc (20ml), which was washed with saturated aqueous $NaHCO_3$ (20ml). Using dilute HCl, the aqueous phase was acidified to pH 2 and the precipitate extracted into EtOAc (50ml).

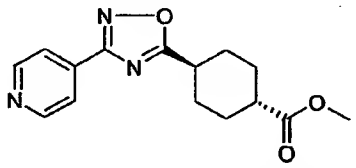
The organic phase was dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography (5% AcOH in IH-EtOAc, 7:3 to 1:1) to afford the title acid: RT = 2.89min; *m/z* ($ES^+$) = 260.3 $[M+H]^+$.

**Preparation 2**: 2-Chloro-*N*-hydroxyisonicotinamidine



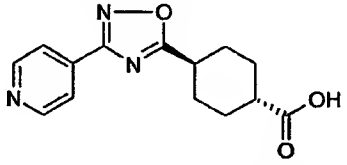
A solution of sodium carbonate (382mg, 3.61mmol) and ammonium hydroxide hydrochloride salt (502mg, 7.22mmol) in water (10ml) was added to 2-chloro-4-cyanopyridine (1.0g, 7.22mmol) and the mixture heated to 80°C. Sufficient ethanol (10ml) was then added to give a homogeneous solution. After 18h, the solution was cooled and the ethanol removed *in vacuo*. The solid precipitate was collected by filtration, washed with ethanol and $CH_2Cl_2$ then dried, affording the title compound: RT = 0.86min; *m/z* ($ES^+$) = 172.1 $[M+H]^+$.

**Preparation 3**: *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester



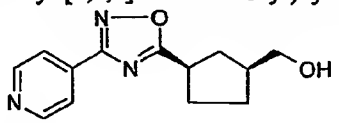
A solution of cyclohexane-1,4-dicarboxylic acid monomethyl ester (1.053g, 5.66mmol) and triethylamine (800µl, 5.66mmol) in toluene (30ml) was cooled to 0°C and isobutylchloroformate (735µl, 5.66mmol) introduced dropwise. The mixture was stirred at rt for 30min whereupon activated, powdered 3Å molecular sieves (5g) and *N*-hydroxyisonicotinamidine (705mg, 5.14mmol) were added. The mixture was heated under reflux for 18h, cooled and filtered through celite. The solvent was removed *in vacuo* and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.20min; *m/z* ($ES^+$) = 288.2 $[M+H]^+$.

**Preparation 4**: *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid



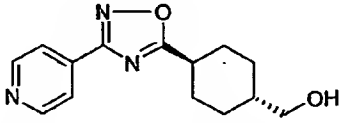
Water (0.5ml) and lithium hydroxide (9.2mg, 0.22mmol) were added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester (**Preparation 3**, 30mg, 104µmol) in THF (1.5ml). The mixture was heated at 60°C for 1.5h, cooled and the THF removed *in vacuo*. Water (5ml) was added, the aqueous washed with EtOAc (5ml) and carefully acidified with 1M HCl to pH 4. The resulting precipitate was extracted into 3% MeOH in EtOAc (2x15ml) and the combined organic phases dried ($MgSO_4$) and evaporated to afford the title compound: RT = 2.74min, *m/z* ($ES^+$) = 274.2 $[M+H]^+$.

**Preparation 5:** *cis*-[3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol



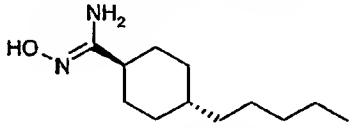
Sodium hydride (100mg of a 60% dispersion in oil, 2.5mmol) was added to a solution of *N*-hydroxyisonicotinamidine (344mg, 2.5mmol) in anhydrous THF (3ml) and the mixture heated under reflux for 1h. *cis*-Methyl-3-hydroxymethylcyclopentane-1-carboxylate (396mg, 2.5mmol) was added in one portion and heating was continued for 18h. After cooling, the solution was filtered through celite and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 2.59min, *m/z* ($ES^+$) = 246.1 $[M+H]^+$.

**Preparation 6:** *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol



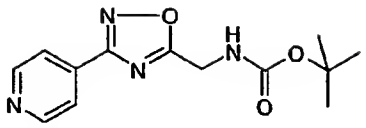
A solution of *trans*-4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester (**Preparation 3**, 200mg, 0.696mmol) in dry $CH_2Cl_2$ (13ml) was cooled to -30°C and diisobutylaluminium hydride (1.59ml of a 1M solution in toluene, 1.59mmol) introduced dropwise. After 30min the reaction was quenched with 2M HCl (6ml), the mixture warmed to rt and partitioned between 2M HCl (10ml) and $CH_2Cl_2$ (10ml). The aqueous phase was neutralised using 2M NaOH then extracted with $CH_2Cl_2$ (4x20ml). The combined organics were dried ($MgSO_4$) and evaporated to afford the title compound: RT = 2.59min, *m/z* ($ES^+$) = 260.2 $[M+H]^+$.

**Preparation 7:** *trans-N*-Hydroxy-4-pentylcyclohexylamidine



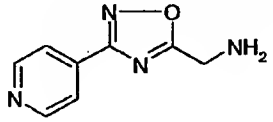
A solution of potassium carbonate (2.49g, 18mmol) and $NH_2OH.HCl$ (2.50g, 36mmol) in water (15ml) was added to *trans*-4-pentylcyclohexanecarbonitrile (4.30g, 24mmol) and the mixture heated to 80°C. Sufficient ethanol (approx. 45ml) was then added to give a homogeneous solution. After 10h, the solution was cooled, diluted with water (200ml) and the solid material collected by filtration. The solid was dissolved in EtOAc (150ml) and the resulting solution washed with brine (50ml) and dried ($MgSO_4$). The solvent was reduced in volume to 15ml and hexane (60ml) added to precipitate the title compound, which was collected by filtration: RT = 2.86min, *m/z* ($ES^+$) = 213.2 $[M+H]^+$.

**Preparation 8:** (3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)carbamic acid *tert*-butyl ester



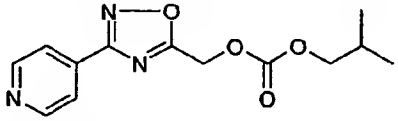
A solution of *tert*-butoxycarbonylaminoacetic acid (1.0g, 5.71mmol) and triethylamine (802µl, 5.71mmol) in toluene (30ml) was cooled to 0°C and isobutylchloroformate (740µl, 5.71mmol) introduced dropwise. The reaction mixture was stirred at 0°C for 10min and at rt for 30min, whereupon *N*-hydroxyisonicotinamidine (652mg, 4.76mmol) and powdered 3Å molecular sieves (4g) were added. After heating under reflux for 12h the reaction was cooled, filtered through celite and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (200ml) and washed with water (30ml) and saturated aqueous $NaHCO_3$ (30ml), then dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 2:3) to afford the title compound: RT = 2.97 min; *m/z* ($ES^+$) = 277.1 $[M+H]^+$.

**Preparation 9**: *C*-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methylamine



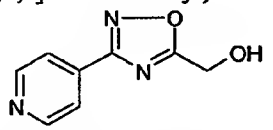
Trifluoroacetic acid (6.5ml) was added to a solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)carbamic acid *tert*-butyl ester (**Preparation 8**, 420mg, 1.52mmol in $CH_2Cl_2$ (10ml) and the mixture stirred at rt for 2h. The solvent was evaporated and the residue dissolved in EtOAc (100ml). After washing with saturated aqueous $Na_2CO_3$ (25ml), the aqueous phase was re-extracted with 5% MeOH in $CH_2Cl_2$ (7x25ml) and the combined organic phases dried ($MgSO_4$). The solvent was removed to afford the title compound: RT = 0.25min; *m/z* ($ES^+$) = 177.1 $[M+H]^+$.

**Preparation 10**: 3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylcarbonic acid isobutyl ester



Isobutylchloroformate (11.67ml, 90mmol) was added to a solution of hydroxyacetic acid (3.42g, 45mmol) and triethylamine (12.65ml, 90mmol) in toluene (220ml) at 0°C. After stirring at rt for 1h, *N*-hydroxyisonicotinamidine (6.17g, 45mmol) and powdered 3Å molecular sieves (20g) were added. After heating under reflux for 18h, the cooled mixture was filtered through celite, the solvent evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.51min; *m/z* ($ES^+$) = 278.0 $[M+H]^+$.

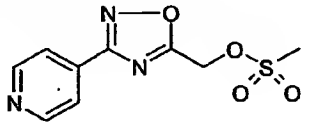
**Preparation 11**: (3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol



A stirred solution of 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylcarbonic acid isobutyl ester (**Preparation 10**, 5.94g, 21.45mmol) in methanol (75ml) at rt was treated with 2M

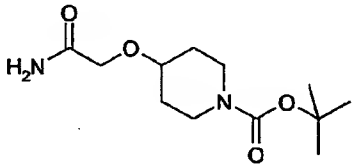
aqueous sodium hydroxide (11.8ml, 23.6mmol). After 10min the solvent was removed and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 1.30min; *m/z* ($ES^+$) = 178.0 $[M+H]^+$.

**Preparation 12**: Methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester



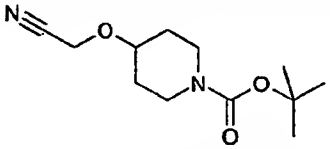
Methanesulfonyl chloride (0.50ml, 6.50mmol) was added to a stirred solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol (1g, 5.65mmol) and triethylamine (0.953ml, 6.78mmol) in $CH_2Cl_2$ (30ml) at 0°C. After 10min, water (20ml) was added and the aqueous phase extracted with $CH_2Cl_2$ (20ml). The combined organic phases were dried ($MgSO_4$) and evaporated to afford the title compound: RT = 2.32min; *m/z* ($ES^+$) = 256.0 $[M+H]^+$.

**Preparation 13**: 4-Carbamoylmethoxypiperidine-1-carboxylic acid *tert*-butyl ester



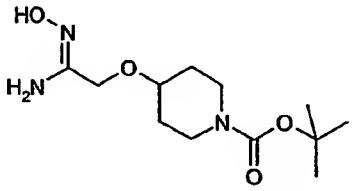
A solution of 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 14.13g, 54.7mmol) and triethylamine (7.68ml, 65.6mmol) in anhydrous THF (250ml) was cooled to 0°C and isobutylchloroformate (8.51ml, 65.6mmol) introduced dropwise. After stirring at 0°C for 30min, the reaction mixture was cooled to -20°C and added rapidly via cannula to a solution of 0.7M ammonia in anhydrous $CH_2Cl_2$ (250ml, 180mmol) at -70°C. The reaction was allowed to warm to rt and stirred for 1h. The mixture was diluted with $CH_2Cl_2$ (250ml) and washed with saturated aqueous $NaHCO_3$ (200ml), 0.5M HCl (200ml) and brine (200ml) then dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography (IH-THF 3:7) to afford the title compound: $\delta_H$ ($CDCl_3$) 1.49 (9H, s), 1.53-1.60 (2H, m), 1.85-1.92 (2H, m), 3.11 (2H, m), 3.58 (1H, m), 3.76-3.83 (2H, m), 3.98 (2H, s), 6.19 (1H, bs), 6.56 (1H, bs).

**Preparation 14**: 4-Cyanomethoxypiperidine-1-carboxylic acid *tert*-butyl ester



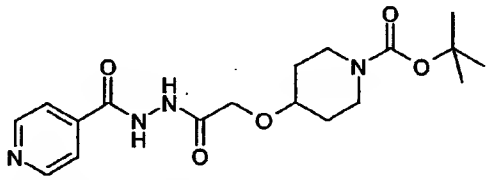
A solution of 4-carbamoylmethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 13**, 235mg, 0.91mmol) and triethylamine (140µl, 1mmol) in anhydrous $CH_2Cl_2$ (5ml) was cooled to 0°C and a solution of trichloroacetyl chloride (174mg, 0.96mmol) in anhydrous $CH_2Cl_2$ added dropwise. The reaction mixture was stirred at rt for 1h, the solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: $\delta_H$ ($CDCl_3$) 1.50 (9H, s), 1.58-1.65 (2H, m), 1.89-1.95 (2H, m), 3.20 (2H, m), 3.74-3.79 (3H, m), 4.33 (2H, s).

**Preparation 15**: 4-(*N*-Hydroxycarbamimidoylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



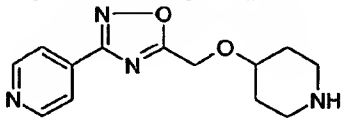
A solution of potassium carbonate (119mg, 0.86mmol) and $NH_2OH.HCl$ (119mg, 1.71mmol) in water (0.5ml) was added to 4-cyanomethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 14**, 206mg, 0.857mmol) in ethanol (2ml). The mixture was heated at 75°C for 0.75h, cooled and the ethanol evaporated. The residue was diluted with EtOAc (50ml) and washed with water (2x10ml) and brine (10ml) then dried ($MgSO_4$). The solvent was removed to afford the title compound: $\delta_H$ ($CDCl_3$) 1.50 (9H, s), 1.50-1.60 (2H, m), 1.85-1.92 (2H, m), 3.13 (2H, m), 3.56 (1H, m), 3.77-3.84 (2H, m), 4.05 (2H, s), 4.82 (2H, bs); RT = 2.70min, *m/z* ($ES^+$) = 274.0 $[M+H]^+$.

**Preparation 16**: 4-{2-Oxo-2-[*N'*-(pyridine-4-carbonyl)hydrazino]ethoxy}piperidine-1-carboxylic acid *tert*-butyl ester



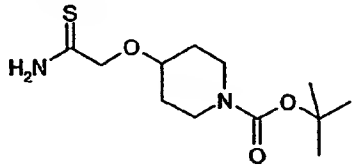
A solution of 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 1.25g, 4.82mmol), ethyl-(3-dimethylaminopropyl)carbodiimide (924mg, 4.82mmol) and *N*-hydroxybenzotriazole (651mg, 4.82mmol) in anhydrous $CH_2Cl_2$ (30ml) were stirred at rt for 10min. Isonicotinic acid hydrazide (601mg, 4.38mmol) was added in one portion and stirring continued for a further 18h. The reaction mixture was diluted with $CH_2Cl_2$ (150ml) and washed with water (30ml), saturated aqueous $NaHCO_3$ (30ml) and brine (30ml). After drying ($MgSO_4$) the solvent was removed to afford the title compound: RT = 2.89min; *m/z* ($ES^+$) = 379.1 $[M+H]^+$.

**Preparation 17**: 4-[5-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine



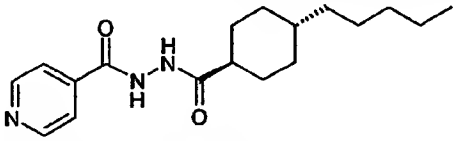
The *tert*-butoxycarbonyl group of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 1**) was removed using the procedure described in **Example 51**, affording the title compound: RT = 1.84min; *m/z* ($ES^+$) = 261.2 $[M+H]^+$.

**Preparation 18**: 4-Thiocarbamoylmethoxypiperidine-1-carboxylic acid *tert*-butyl ester



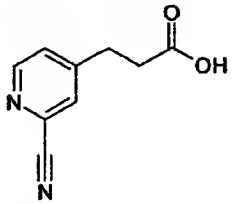
A solution of 4-carbamoylmethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 13**, 67.5mg, 260μmol) and Lawesson's reagent (116mg, 287μmol) in dimethoxyethane (1.5ml) was stirred at rt for 24h. The solvent was evaporated and the residue purified by flash chromatography (5%MeOH in $CH_2Cl_2$) to afford the title compound: $\delta_H$ ($CDCl_3$) 1.50 (9H, s), 1.55-1.63 (2H, m), 1.88-1.95 (2H, m), 3.12 (2H, ddd), 3,59-3.66 (1H, m), 3.79-3.87 (2H, m), 4.40, (2H, s), 7.65 (1H, bs), 8.04 (1H, bs).

**Preparation 19**: *trans*-4-Pentyl-cyclohexanecarboxylic acid *N'*-(pyridine-4-carbonyl)hydrazide



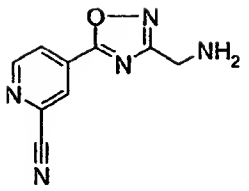
Isonicotinic acid hydrazide was reacted with 4-pentylcyclohexane carboxylic acid in a similar fashion to that described in **Preparation 16** to afford the title compound: RT = 4.79min; *m/z* ($ES^+$) = 318.0 $[M+H]^+$.

**Preparation 20**: 3-(2-Cyanopyridin-4-yl)propionic acid



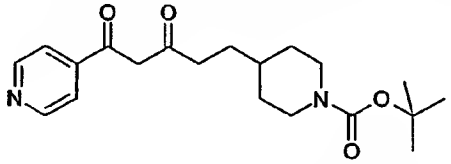
A solution of $K_2CO_3$ (1.67g, 12.1mmol) in $H_2O$ (30ml) was added to a stirred solution of 3-(2-cyanopyridin-4-yl)propyl acetate (4.94g, 24.2mmol) in MeOH (130ml). After 25min, the MeOH was removed under reduced pressure, then the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a residue that was purified by column chromatography (IH–EtOAc, 1:3) to furnish 4-(3-hydroxypropyl)pyridine-2-carbonitrile: *m/z* ($ES^+$) = 163.1 $[M+H]^+$. A solution of this alcohol (500mg, 3.1mmol) in DMF (20ml) was treated with PDC (7g, 18.6mmol) and $H_2O$ (0.5ml). The reaction was stirred for 16h, before being partitioned between $H_2O$ and EtOAc. The aqueous phase was extracted twice with EtOAc, then the combined organic extracts were washed with brine, before being dried ($MgSO_4$), filtered, and concentrated to give the title compound: *m/z* ($ES^+$) = 177.0 $[M+H]^+$.

**Preparation 21**: 4-(3-Aminomethyl-[1,2,4]oxadiazol-5-yl)pyridine-2-carbonitrile



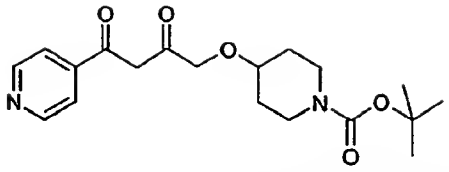
$NEt_3$ (6.6ml, 47.3mmol) was added to a stirred solution of 2-cyanoisonicotinic acid (7.00g, 47.3mmol) in toluene (500ml). The mixture was cooled to 0°C, before being treated with isobutyl chloroformate (6.1ml, 47.3mmol). Stirring was continued at 0°C for 10 min, then the mixture was allowed to warm to rt over 1h, before being treated with (*N*-hydroxycarbamimidoylmethyl)carbamic acid *tert*-butyl ester (7.44g, 39.4mmol) and dried 4Å molecular sieves (40g). The reaction was heated under reflux for 16h. On cooling, the mixture was filtered through celite, washing with MeOH. The combined filtrates were concentrated in vacuo, then the residue was dissolved in EtOAc. The EtOAc solution was washed with saturated aqueous $Na_2CO_3$ and brine, before being dried ($MgSO_4$). Filtration, solvent evaporation, and column chromatography (IH–EtOAc, 7:3) furnished [5-(2-cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethyl]carbamic acid *tert*-butyl ester: *m/z* ($ES^+$) = 603.2 $[2M+H]^+$. A stirred solution of this carbamate (1.95g, 6.5mmol) in $CHCl_3$ (50ml) was treated with TMS–I (2.2ml, 15.6mmol). After 10min, the reaction was treated with MeOH (2.5ml, 62.2mmol), then stirring was continued for a further 10min. The solvents were evaporated off under reduced pressure, then the residue was dissolved in MeOH and adsorbed onto $SiO_2$. Column chromatography (EtOAc then EtOAc–MeOH, 9:1) afforded the title compound: *m/z* ($ES^+$) = 202.0 $[M+H]^+$.

**Preparation 22**: 4-(3,5-Dioxo-5-pyridin-4-ylpentyl)piperidine-1-carboxylic acid *tert*-butyl ester



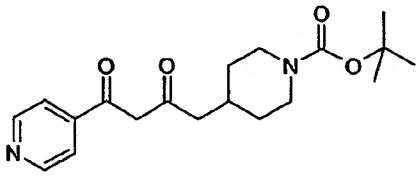
CDI (0.63g, 3.9mmol) was added to a solution of 4-(2-carboxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester (1.00g, 3.9mmol) in anhydrous THF (7.6ml), then the mixture was stirred for 45min. In a separate vessel, 4-acetylpyridine (0.49g, 4.1mmol) was added slowly to a stirred solution of LDA (2.04ml of a 2.0M solution in heptane–THF–ethylbenzene, 4.1mmol) in anhydrous THF (15.3ml) at –78°C. After 45 min, the solution of the acylimidazole was added slowly via cannula to the lithiated 4-acetylpyridine while maintaining the temperature at –78°C. The reaction was allowed to warm to rt over 2h, before being diluted with EtOAc (150ml). The solution was washed with 10% aqueous citric acid (2 × 15ml), saturated aqueous $NaHCO_3$ (2 × 15ml), and brine (20ml), before being dried ($MgSO_4$). Filtration, concentration, and purification by RP-HPLC afforded the title compound: *m/z* ($ES^+$) = 261.2 $[M–Boc+H]^+$.

**Preparation 23**: 4-(2,4-Dioxo-4-pyridin-4-ylbutoxy)piperidine-1-carboxylic acid *tert*-butyl ester



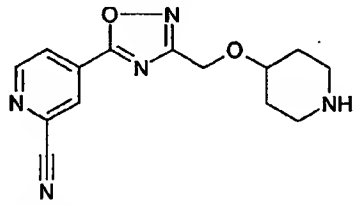
Condensation of 4-acetylpyridine with 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**), employing the protocol described in **Preparation 22**, afforded the title compound: *m/z* ($ES^+$) = 263.2 $[M–Boc+H]^+$.

**Preparation 24:** 4-(2,4-Dioxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



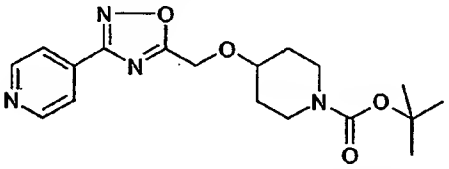
Condensation of 4-acetylpyridine with 4-carboxymethylpiperidine-1-carboxylic acid *tert*-butyl ester, utilising the protocol described in **Preparation 22**, afforded the title compound: *m/z* ($ES^+$) = 247.2 $[M–Boc+H]^+$.

**Preparation 25:** 4-[3-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile



To a stirred solution of 4-[5-(2-cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester (**Example 42**, 2.0g, 5.2mmol) in chloroform (100ml) under argon, was added trimethylsilyl iodide (2.95ml, 20.8mmol) and the reaction mixture stirred for 1h. MeOH was added until a solution formed then sodium thiosulphate (6.6g, 41.5mmol) was added and the reaction mixture stirred vigorously for 10min. The solids were removed by filtration and the filtrate adsorbed onto silica gel. Purification via column chromatography (DCM-MeOH, 9:1) afforded the title compound: RT = 1.92min; *m/z* ($ES^+$) = 286.0 $[M+H]^+$.

**Example 1:** 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester

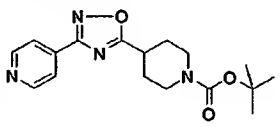
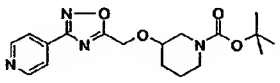
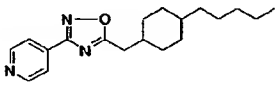
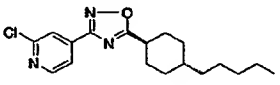
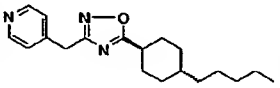


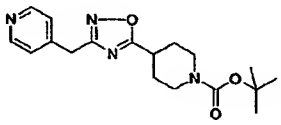
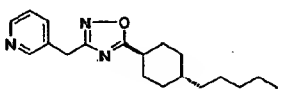
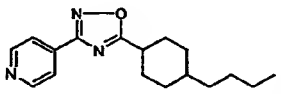
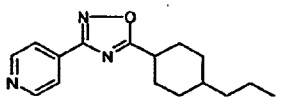
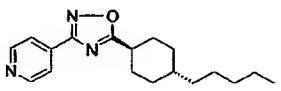
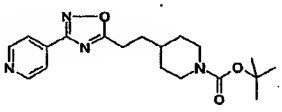
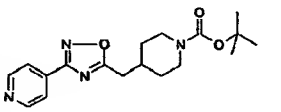
A stirred solution of triethylamine (123µl, 0.87mmol) and 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 227mg, 0.87mmol) in toluene (10ml) was

treated with isobutylchloroformate (113µl, 0.87mmol). After 20min, activated powdered 3Å molecular sieves (0.7g) and *N*-hydroxyisonicotinamidine (100mg, 0.73mmol) were added and the mixture heated under reflux for 18h. On cooling, the mixture was filtered through celite, the solvent removed *in vacuo* and the residue purified by flash chromatography (IH-EtOAc, 7:13) to afford the title compound: RT = 3.29min; *m/z* ($ES^+$) 361.3 $[M+H]^+$; $\delta_H$ ($CDCl_3$) 1.40 (9H, s), 1.55-1.63 (2H, m), 1.80-1.92 (2H, m), 3.05-3.15 (2H, m), 3.64-3.79 (3H, m), 4.80 (2H, s), 7.90 (2H, d), 8.75 (2H, d).

The [1,2,4]oxadiazoles in Table 1 were synthesised from the appropriate amidoxime and the corresponding acid, in a similar manner to that described in **Example 1.**

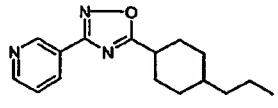
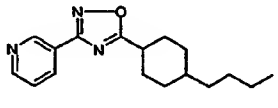
**Table 1**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 2 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester | 3.52 | 331.3 $[M+H]^+$ |
| 3 |  | 3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester | 3.29 | 361.3 $[M+H]^+$ |
| 4 |  | 4-[5-(4-Pentylcyclohexylmethyl)-[1,2,4]oxadiazol-3-yl]pyridine | 4.97 | 314.3 $[M+H]^+$ |
| 5 |  | *trans*-2-Chloro-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine | 5.19 | 334.3 $[M+H]^+$ |
| 6 |  | *trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-ylmethyl]pyridine | 3.77 | 314.3 $[M+H]^+$ |

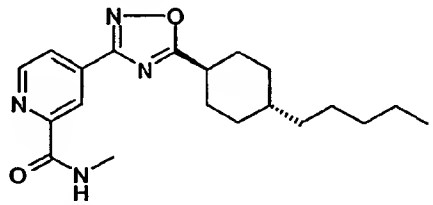
| | | | | |
|---|---|---|---|---|
| 7 |  | 4-(3-Pyridin-4-ylmethyl [1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester | 2.67 | 345.2 $[M+H]^+$ |
| 8 |  | *trans*-3-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-ylmethyl]pyridine | 3.92 | 314.3 $[M+H]^+$ |
| 9 |  | 4-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine | 4.69 | 286.2 $[M+H]^+$ |
| 10 |  | 4-[5-(4-*n*-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine | 4.42 | 272.3 $[M+H]^+$ |
| 11 |  | *trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine | 4.87 | 300.3 $[M+H]^+$ |
| 12 |  | 4-[2-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-ethyl]piperidine-1-carboxylic acid *tert*-butyl ester | 3.84 | 359.2 $[M+H]^+$ |
| 13 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester | 3.67 | 345.2 $[M+H]^+$ |

The compounds in Table 2 were also prepared according to the method described in **Example 1**.

Table 2

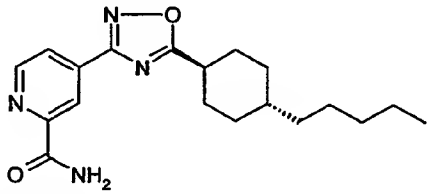
| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 14 |  | 3-[5-(4-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine | 4.42 | 272.3 $[M+H]^+$ |
| 15 |  | 3-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine | 4.76 | 286.3 $[M+H]^+$ |

**Example 16**: *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carboxylic acid methylamide



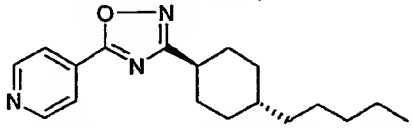
A stirred solution of *trans*-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine (**Example 11**, 100mg, 0.33mmol) and $H_2SO_4$ (17.8µl, 0.33mmol) in *N*-methylformamide (2ml) was cooled to 0°C. Solid $FeSO_4.7H_2O$ (23mg, 83µmol) was added followed by $H_2O_2$ (63µl of a 27% solution in water, 0.5mmol) and the mixture stirred at 0°C for 2h. A solution of 1M aqueous sodium citrate (1ml) was added and the mixture extracted with $CH_2Cl_2$ (2x5ml). The combined organic phases were washed with water (2x5ml), saturated aqueous $NaHCO_3$ (2x5ml) and brine (5ml) then dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 17:3 to 7:3) to afford the title compound: RT = 4.86min, *m/z* ($ES^+$) = 357.4 $[M+H]^+$.

**Example 17**: *trans*-4-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine-2-carboxylic acid amide



A stirred solution of *trans*-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine (**Example 11**) and $H_2SO_4$ in formamide was treated with $FeSO_4.7H_2O$ and $H_2O_2$ in a similar way to that described in **Example 16** to afford the title compound: RT = 4.66min, *m/z* ($ES^+$) = 343.4 $[M+H]^+$.

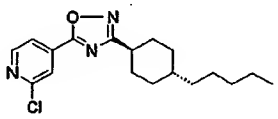
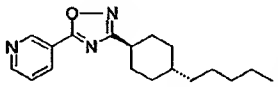
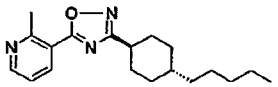
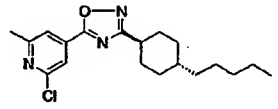
**Example 18:** *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine

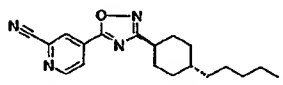
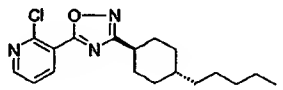
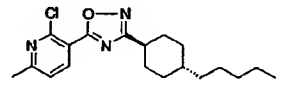
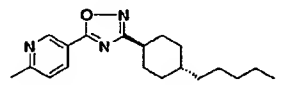
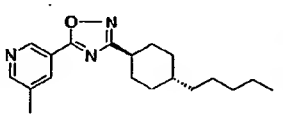
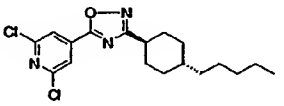
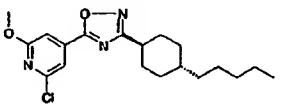
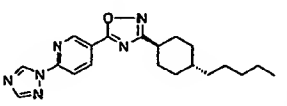


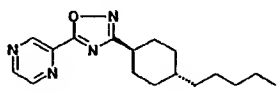
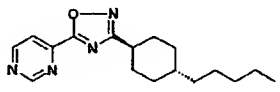
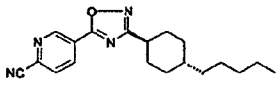
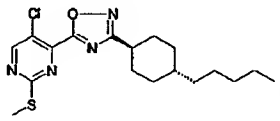
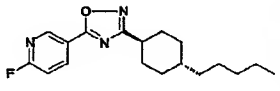
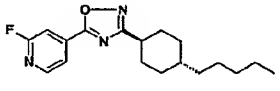
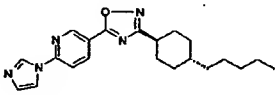
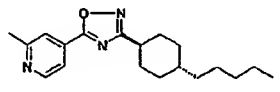
A solution of isonicotinic acid (36.2mg, 290μmol) and triethylamine (30mg, 290μmol) in anhydrous THF (3ml) was cooled to 0°C and isobutylchloroformate (39mg, 280μmol) was added. The mixture was stirred at rt for 1h and solid *trans*-*N*-hydroxy-4-pentylcyclohexylamidine (**Preparation 7**, 50mg, 235μmol) added in one portion. After 45min the reaction was diluted with EtOAc (12ml), washed with saturated aqueous $NaHCO_3$ (3ml) and brine (6ml), then dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in toluene (5ml) and solution heated under gentle reflux for 2h. The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 2:1) to afford the title compound: RT = 4.97min; *m/z* ($ES^+$) = 300.3 $[M+H]^+$.

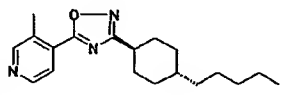
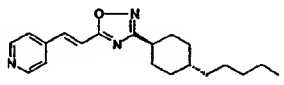
The [1,2,4]oxadiazoles in Table 3 were synthesized by reacting the appropriate acid with *trans*-*N*-hydroxy-4-pentylcyclohexylamidine (**Preparation 7**), in a manner similar to that described in **Example 18**.

**Table 3**

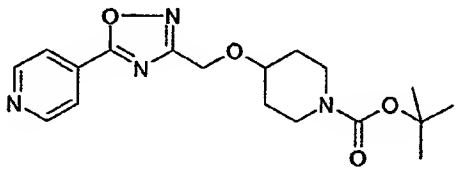
| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 19 |  | *trans*-2-Chloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.14 | 334.3 $[M+H]^+$ |
| 20 |  | *trans*-3-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.11 | 300.3 $[M+H]^+$ |
| 21 |  | *trans*-2-Methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 4.92 | 314.3 $[M+H]^+$ |
| 22 |  | *trans*-2-Chloro-6-methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl] pyridine | 5.39 | 348.3 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 23 |  | *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile | 4.91 | 366.4 $[M+H+CH_3CN]^+$ |
| 24 |  | *trans*-2-Chloro-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 4.99 | 334.3 $[M+H]^+$ |
| 25 |  | *trans*-2-Chloro-6-methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.34 | 348.3 $[M+H]^+$ |
| 26 |  | *trans*-2-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 4.80 | 314.3 $[M+H]^+$ |
| 27 |  | *trans*-3-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 4.94 | 314.3 $[M+H]^+$ |
| 28 |  | *trans*-2,6-Dichloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.37 | 368.3 $[M+H]^+$ |
| 29 |  | *trans*-2-Chloro-6-methoxy-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.44 | 364.3 $[M+H]^+$ |
| 30 |  | *trans*-5-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]-2-[1,2,4]triazol-1-ylpyridine | 5.36 | 367.4 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| **31** |  | 2-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrazine | 4.72 | 301.2 $[M+H]^+$ |
| **32** |  | 4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine | 4.86 | 301.2 $[M+H]^+$ |
| **33** |  | *trans*-5-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile | 5.16 | 325.2 $[M+H]^+$ |
| **34** |  | *trans*-5-Chloro-2-methylsulfanyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine | 5.32 | 381.1 $[M+H]^+$ |
| **35** |  | *trans*-2-Fluoro-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.12 | 318.2 $[M+H]^+$ |
| **36** |  | *trans*-2-Fluoro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.07 | 318.2 $[M+H]^+$ |
| **37** |  | *trans*-2-Imidazol-1-yl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 4.49 | 366.2 $[M+H]^+$ |
| **38** |  | *trans*-2-Methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.05 | 314.2 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 39 |  | *trans*-3-Methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine | 5.16 | 314.2 $[M+H]^+$ |
| 40 |  | *trans*-4-{2-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl] vinyl}pyridine | 4.62 | 326.2 $[M+H]^+$ |

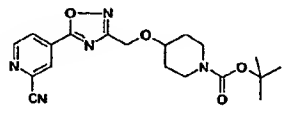
**Example 41:** 4-(5-Pyridin-4-yl-[1,2,4]oxadiazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester

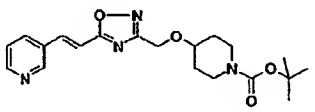
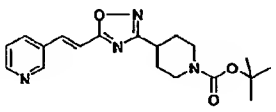
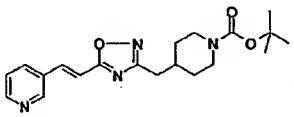
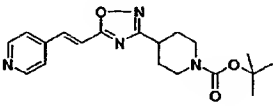
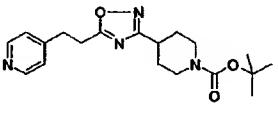
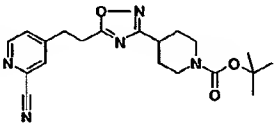
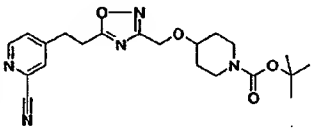
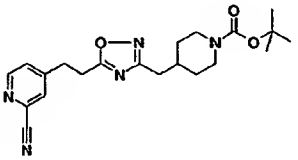


A solution of isonicotinic acid (31mg, 250µmol) and triethylamine (51mg, 500 µmol) in anhydrous THF was cooled to 0°C and isobutylchloroformate (34mg, 250µmol) was added. The reaction was stirred at rt for 0.5h and solid 4-(*N*-hydroxycarbamimidoylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 15**, 54.5mg, 200µmol) added in one portion. After stirring for 40min the solvent was removed, EtOAc added to the residue, and the mixture passed through a small plug of silica, eluting with EtOAc. Following evaporation, the residue was dissolved in toluene (4ml) and heated under reflux for 15h. The solvent was then evaporated and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 3.65min, *m/z* ($ES^+$) = 361.2 $[M+H]^+$.

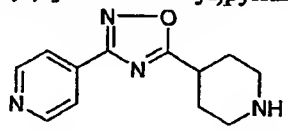
The [1,2,4]oxadiazoles in Table 4 were synthesized by condensing the appropriate acid with a suitable amidoxime, in a manner similar to that described in **Example 41**.

**Table 4**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 42 |  | 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester | 3.82 | 386.1 $[M+H]^+$ |

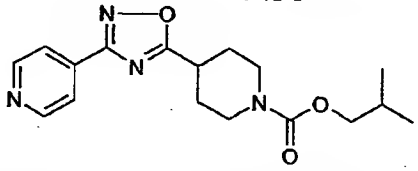
| | | | | |
|---|---|---|---|---|
| 43 |  | (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester | 3.49 | 387.2 $[M+H]^+$ |
| 44 |  | (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester | 3.52 | 357.2 $[M+H]^+$ |
| 45 |  | (*E*)-4-[5-(2-Pyridin-3-yl-vinyl)-[1,2,4]oxadiazol-3-ylmethyl]piperidine-1-carboxylic acid *tert*-butyl ester | 3.62 | 271.2 $[M-Boc+H]^+$ |
| 46 |  | (*E*)-4-[5-(2-Pyridin-4-yl-vinyl)-[1,2,4]oxadiazol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester | 3.26 | 357.2 $[M+H]^+$ |
| 47 |  | 4-[5-(2-Pyridin-4-yl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester | 2.76 | 359.1 $[M+H]^+$ |
| 48 |  | 4-{5-[2-(2-Cyanopyridin-4-yl)ethyl]-[1,2,4]oxadiazol-3-yl}piperidine-1-carboxylic acid *tert*-butyl ester | 3.70 | 384.2 $[M+H]^+$ |
| 49 |  | 4-{5-[2-(2-Cyanopyridin-4-yl)ethyl]-[1,2,4]oxadiazol-3-ylmethoxy}piperidine-1-carboxylic acid *tert*-butyl ester | 3.74 | 414.2 $[M+H]^+$ |
| 50 |  | 4-{5-[2-(2-Cyanopyridin-4-yl)ethyl]-[1,2,4]oxadiazol-3-ylmethyl}piperidine-1-carboxylic acid *tert*-butyl ester | 3.76 | 398.2 $[M+H]^+$ |

**Example 51**: 4-(5-Piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine



Trifluoroacetic acid (20ml) was added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 2**, 1.64g, 4.96mmol) in $CH_2Cl_2$ (35ml). After 2.5h at rt, the solvent was evaporated under reduced pressure. The residual solid was suspended in EtOAc (150ml) and washed with saturated aqueous $Na_2CO_3$ (20ml). The aqueous was separated and extracted with EtOAc (3x30ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound: RT = 3.48min, *m/z* ($ES^+$) = 231.2 $[M+H]^+$.

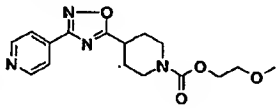
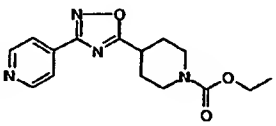
**Example 52**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid isobutyl ester



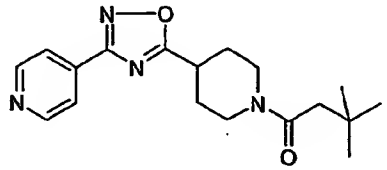
A solution of pyridine (18µl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (**Example 51**, 50mg, 0.22mmol) in $CH_2Cl_2$ (4ml) was treated with isobutylchloroformate (54mg, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 3.42min, *m/z* ($ES^+$) = 331.2 $[M+H]^+$.

The [1,2,4]oxadiazoles in Table 4 were synthesized in a manner similar to that described in **Example 52**.

**Table 4**

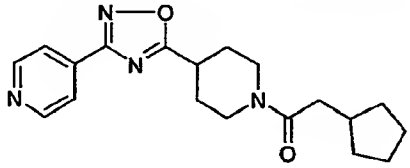
| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 53 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 2-methoxyethyl ester | 2.77 | 333.2 $[M+H]^+$ |
| 54 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ethyl ester | 3.19 | 303.2 $[M+H]^+$ |

**Example 55:** 3,3-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]butan-1-one



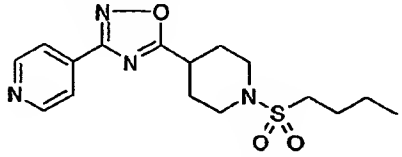
A solution of pyridine (18µl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (**Example 51**, 50mg, 0.22mmol) in $CH_2Cl_2$ (4ml) was treated with 3,3-dimethylbutanoyl chloride (58mg, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 3.11min, *m/z* ($ES^+$) = 329.3 $[M+H]^+$.

**Example 56:** 2-Cyclopentyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]ethanone



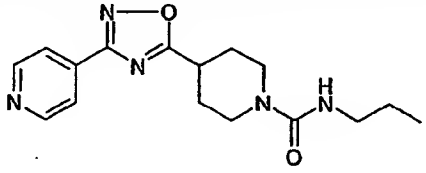
4-[5-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Example 51**) was reacted with cyclopentylacetyl chloride, in a similar manner to that described in **Example 55**, to afford the title compound: RT = 3.44min, *m/z* ($ES^+$) = 341.3 $[M+H]^+$.

**Example 57:** 4-{5-[1-(Butane-1-sulfonyl)piperidin-4-yl]-[1,2,4]oxadiazol-3-yl}pyridine



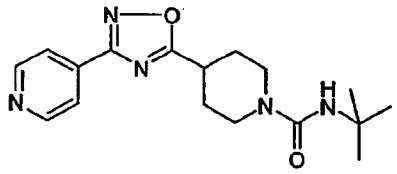
A solution of pyridine (18µl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (**Example 51**, 50mg, 0.22mmol) in $CH_2Cl_2$ (4ml) was treated with butane-1-sulfonyl chloride (56µl, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was dissolved in EtOAc (5ml) and extracted into 2M HCl (10ml). The aqueous phase was then basified using 2M NaOH to pH = 8 and extracted with $CH_2Cl_2$ (2x10ml). The combined organic phases were dried ($MgSO_4$) and evaporated to afford the title compound: RT = 3.29min, *m/z* ($ES^+$) = 351.2 $[M+H]^+$.

**Example 58:** 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid propylamide



1-Propylisocyanate (13μl, 137μmol) was added to a solution of 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (**Example 51**, 15.8mg, 69μmol) in $CH_2Cl_2$ (0.7ml). After stirring 18h at rt, the solvent was removed to afford the title compound: RT = 2.72min; *m/z* ($ES^+$) = 316.3 $[M+H]^+$.

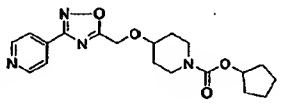
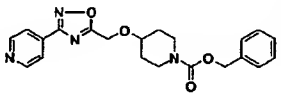
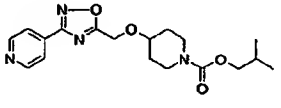
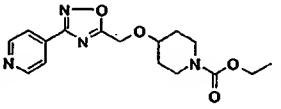
**Example 59**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid *tert*-butylamide

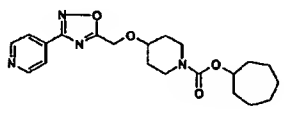
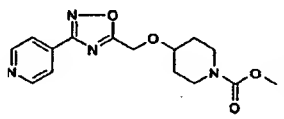
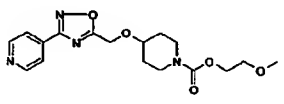
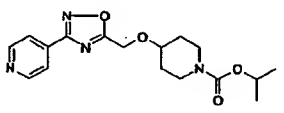
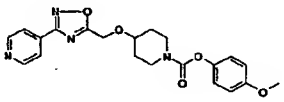
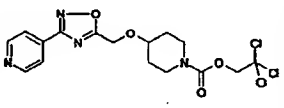
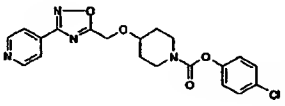
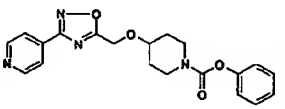


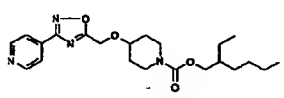
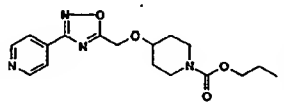
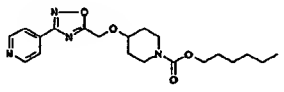
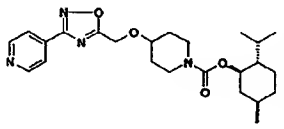
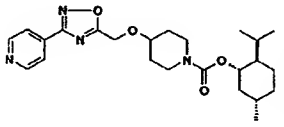
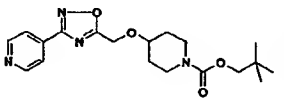
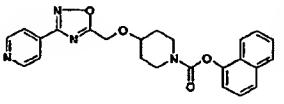
*tert*-Butylisocyanate was reacted with 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (**Example 51**) in a similar fashion to that described in **Example 58** to afford the title compound: RT = 3.04min; *m/z* ($ES^+$) = 330.3 $[M+H]^+$.

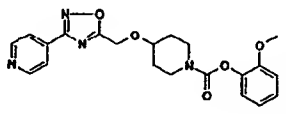
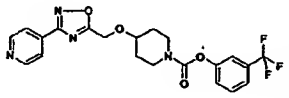
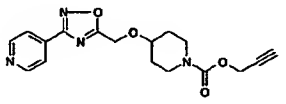
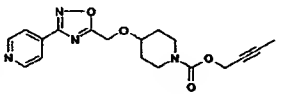
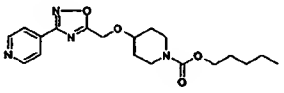
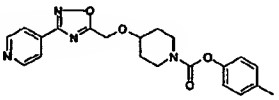
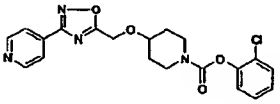
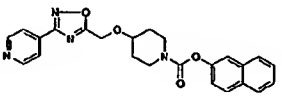
The carbamate esters in Table 5 were produced by reaction of 4-[5-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**) with the appropriate chloroformate, in a fashion similar to that described in **Example 52**.

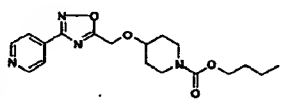
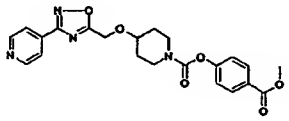
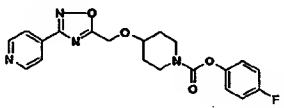
**Table 5**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 60 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester | 3.51 | 373.4 $[M+H]^+$ |
| 61 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid benzyl ester | 3.64 | 395.3 $[M+H]^+$ |
| 62 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid isobutyl ester | 3.49 | 361.3 $[M+H]^+$ |
| 63 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid ethyl ester | 3.03 | 333.3 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 64 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cycloheptyl ester | 3.92 | 401.1 $[M+H]^+$ |
| 65 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid methyl ester | 2.86 | 319.3 $[M+H]^+$ |
| 66 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxy-ethyl ester | 2.95 | 363.2 $[M+H]^+$ |
| 67 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid isopropyl ester | 3.34 | 347.2 $[M+H]^+$ |
| 68 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-methoxy-phenyl ester | 3.74 | 411.1 $[M+H]^+$ |
| 69 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester | 3.81 | 434.8 $[M+H]^+$ |
| 70 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-chloro-phenyl ester | 3.79 | 415.1 $[M+H]^+$ |
| 71 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid phenyl ester | 3.54 | 381.1 $[M+H]^+$ |

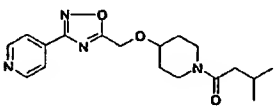
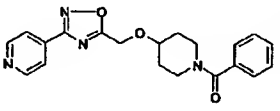
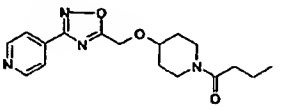
| | | | | |
|---|---|---|---|---|
| 72 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-ethyl-hexyl ester | 4.27 | 417.2 $[M+H]^+$ |
| 73 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid propyl ester | 3.40 | 347.1 $[M+H]^+$ |
| 74 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid hexyl ester | 3.95 | 389.1 $[M+H]^+$ |
| 75 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl ester | 4.44 | 443.2 $[M+H]^+$ |
| 76 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (*1S,2R,5S*)-2-isopropyl-5-methylcyclohexyl ester | 4.39 | 443.2 $[M+H]^+$ |
| 77 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2-dimethylpropyl ester | 3.92 | 375.1 $[M+H]^+$ |
| 78 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-1-yl ester | 3.90 | 431.1 $[M+H]^+$ |

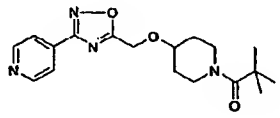
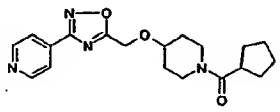
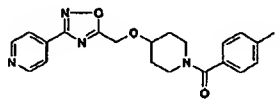
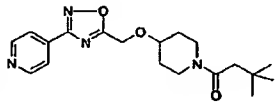
| | | | | |
|---|---|---|---|---|
| 79 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxy-phenyl ester | 3.67 | 411.1 $[M+H]^+$ |
| 80 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 3-trifluoromethylphenyl ester | 3.87 | 449.0 $[M+H]^+$ |
| 81 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid prop-2-ynyl ester | 3.36 | 343.1 $[M+H]^+$ |
| 82 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid but-2-ynyl ester | 3.40 | 357.2 $[M+H]^+$ |
| 83 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid pentyl ester | 3.90 | 375.2 $[M+H]^+$ |
| 84 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *p*-tolyl ester | 3.72 | 395.2 $[M+H]^+$ |
| 85 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-chloro-phenyl ester | 3.72 | 415.1 $[M+H]^+$ |
| 86 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-2-yl ester | 3.97 | 431.1 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 87 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid butyl ester | 3.86 | 361.1 $[M+H]^+$ |
| 88 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-methoxycarbonyl-phenyl ester | 4.64 | 438.9 $[M+H]^+$ |
| 89 |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-fluoro-phenyl ester | 4.66 | 398.9 $[M+H]^+$ |

4-[5-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**) was reacted with the appropriate acid chloride, in a manner similar to that described in **Example 55**, to afford the amides in Table 6.

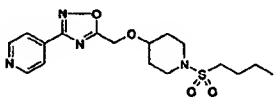
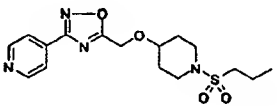
**Table 6**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 90 |  | 3-Methyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]-butan-1-one | 3.04 | 345.2 $[M+H]^+$ |
| 91 |  | Phenyl-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]methanone | 3.29 | 365.2 $[M+H]^+$ |
| 92 |  | 1-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]butan-1-one | 2.90 | 331.2 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 93 |  | 2,2-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]propan-1-one | 3.09 | 345.2 $[M+H]^+$ |
| 94 |  | Cyclopentyl-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]methanone | 3.39 | 357.2 $[M+H]^+$ |
| 95 |  | [4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]-*p*-tolylmethanone | 3.37 | 379.2 $[M+H]^+$ |
| 96 |  | 3,3-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]butan-1-one | 3.29 | 359.1 $[M+H]^+$ |

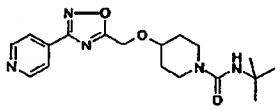
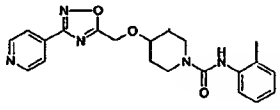
4-[5-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**) was reacted with the appropriate sulfonyl chloride, in a fashion similar to that described in **Example 57**, to afford the sulfonamides in Table 7.

**Table 7**

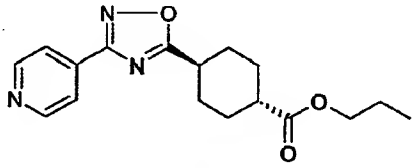
| | | | | |
|---|---|---|---|---|
| 97 |  | 4-{5-[1-(Butane-1-sulfonyl) piperidin-4-yloxymethyl]-[1,2,4]oxadiazol-3-yl}pyridine | 3.34 | 381.2 $[M+H]^+$ |
| 98 |  | 4-{5-[1-(Propane-1-sulfonyl) piperidin-4-yloxymethyl]-[1,2,4]oxadiazol-3-yl}pyridine | 3.12 | 367.1 $[M+H]^+$ |

The compounds in Table 8 were synthesized by reacting 4-[5-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**) with the appropriate isocyanate, in a manner similar to that described in **Example 58.**

**Table 8**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| **99** |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butylamide | 2.95 | 360.4 $[M+H]^+$ |
| **100** |  | 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *o*-tolylamide | 3.44 | 394.4 $[M+H]^+$ |

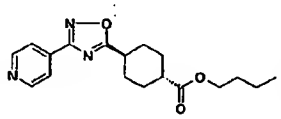
**Example 101**: *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid propyl ester

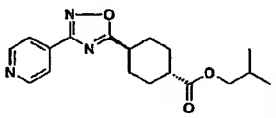


Thionyl chloride (11.5µl, 0.1mmol) was added to a solution of *trans*-4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid (**Preparation 4**, 22mg, 0.08mmol) in 1-propanol (2ml). The mixture was heated under reflux for 2h, cooled and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (10ml), washed with saturated aqueous $NaHCO_3$ (3ml) and brine (5ml), then dried ($MgSO_4$). Removal of the solvent afforded the title compound: RT = 3.67min, *m/z* ($ES^+$) = 316.3 $[M+H]^+$.

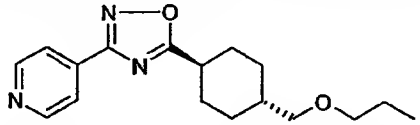
The esters in Table 9 were synthesised in a manner similar to that described in **Example 101.**

**Table 9**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| **102** |  | *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid butyl ester | 3.92 | 330.3 $[M+H]^+$ |

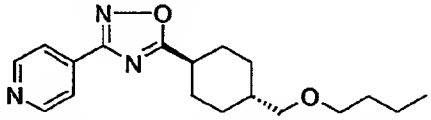
| | | | | |
|---|---|---|---|---|
| 103 |  | *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid isobutyl ester | 3.94 | 330.3 $[M+H]^+$ |

**Example 104:** *trans*-4-[5-(4-Propoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



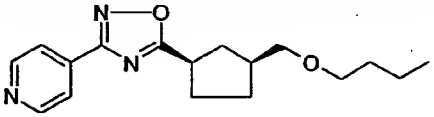
A solution of *trans*-4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol (**Preparation 6**, 50mg, 0.19mmol) in THF (2.5ml) was stirred with sodium hydride (27mg of a 60% dispersion in oil, 0.68mmol) for 1h then 1-bromopropane (70µl, 0.77mmol) and tetrabutylammonium iodide (7mg, 19µmol) were added. The mixture was stirred at rt for 72h, the solvent removed and the residue dissolved in $CH_2Cl_2$ (10ml). After washing with water (3ml), the organic phase was dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography (IH-EtOAc, 7:3) afforded the title compound: RT = 3.92min, *m/z* ($ES^+$) = 302.3 $[M+H]^+$.

**Example 105**: *trans*-4-[5-(4-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



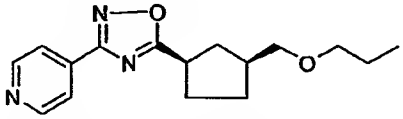
A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol (**Preparation 6**) in THF was treated with sodium hydride, 1-bromobutane and tetrabutylammonium iodide, as described for **Example 104**, to afford the title compound: RT = 4.16min, *m/z* ($ES^+$) = 316.3 $[M+H]^+$.

**Example 106**: *cis*-4-[5-(3-Butoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine



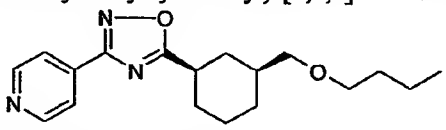
A solution of *cis*-[3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol (**Preparation 5**, 40mg, 0.16mmol) in anhydrous THF (2ml) was treated with sodium hydride (23mg of a 60% dispersion in oil, 0.57mmol) and tetrabutylammonium iodide (6mg, 16µmol). After stirring the mixture at rt for 10min, 1-bromobutane (59µl, 0.65mmol) was introduced and stirring continued for 72h. The solvent was removed *in vacuo*, the residue dissolved in $CH_2Cl_2$ (20ml) and washed with water (2x5ml). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography (IH-EtOAc, 7:3) afforded the title compound: RT = 3.99min, *m/z* ($ES^+$) = 302.3 $[M+H]^+$.

**Example 107:** *cis*-4-[5-(3-Propoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine



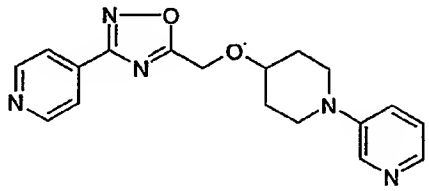
*cis*-[3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol (**Preparation 5**) was reacted with 1-bromopropane in the presence of tetrabutylammonium iodide, using a similar procedure to that described in **Example 106**, to afford the title compound: RT = 3.69min, *m/z* ($ES^+$) = 288.3 $[M+H]^+$.

**Example 108**: *cis*-4-[5-(3-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



*cis*-Methyl-3-hydroxymethylcyclohexane-1-carboxylate was reacted with *N*-hydroxy-isonicotinamidine, using the reaction conditions described in **Preparation 5**, to afford *cis*-[3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexyl]methanol: RT = 2.70min, *m/z* ($ES^+$) = 246.1 $[M+H]^+$. This was subsequently alkylated with 1-bromobutane, under similar conditions to those described in **Example 106**, to afford the title compound: RT = 4.11min, *m/z* ($ES^+$) = 316.3 $[M+H]^+$.

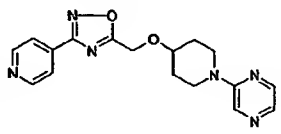
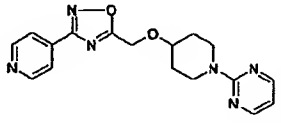
**Example 109**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl



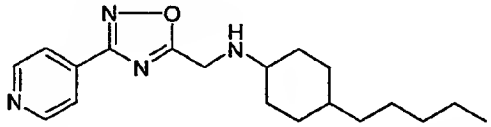
Sodium *tert*-butoxide (86mg, 900μmol) was added to a solution of 3-chloropyridine (23mg, 200μmol), 4-[5-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**, 65mg, 250μmol), $Pd_2dba_3$ (4mg, 4μmol) and 2,8,9-trisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (6mg, 16μmol) in toluene (3ml) and the resulting mixture heated at 80°C for 48h. After cooling and filtering through celite, the solvent was removed and the residue purified by HPLC to afford the title compound: RT = 2.64min; *m/z* ($ES^+$) = 338.0 $[M+H]^+$.

The compounds in Table 10 were prepared in a similar fashion to that described in **Example 109**.

**Table 10**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 110 |  | 2-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrazine | 3.24 | 339.0 $[M+H]^+$ |
| 111 |  | 2-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrimidine | 3.19 | 339.0 $[M+H]^+$ |

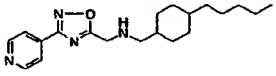
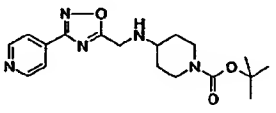
**Example 112:** (4-Pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine

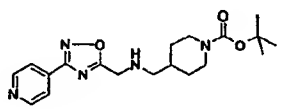
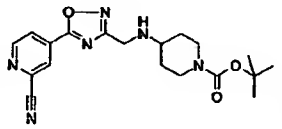


A solution of *C*-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methylamine (**Preparation 9**, 50mg, 284mmol), 4-pentylcyclohexanone (64ml, 340mmol) and sodium triacetoxyborohydride (96mg, 450mmol) in $CH_2Cl_2$ (4ml) were stirred 18h at rt. The reaction was quenched by the addition of 2M aqueous sodium hydroxide (2ml) and the mixture diluted with EtOAc (25ml). The organic phase was separated, washed with brine (5ml) and dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.12min; *m/z* ($ES^+$) = 329.3 $[M+H]^+$.

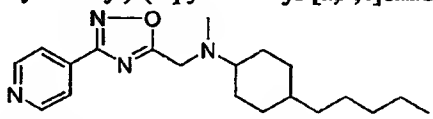
The amines in Table 11 were synthesized in a manner similar to that described in **Example 112**.

**Table 11**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 113 |  | (4-Pentylcyclohexyl-methyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine | 3.19 | 343.2 $[M+H]^+$ |
| 114 |  | 4-[(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 2.42 | 360.2 $[M+H]^+$ |

| | | | | |
|---|---|---|---|---|
| 115 |  | 4-{[(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester | 2.65 | 374.2 $[M+H]^+$ |
| 116 |  | 4-{[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethyl]amino}-piperidine-1-carboxylic acid *tert*-butyl ester | 2.59 | 385.1 $[M+H]^+$ |

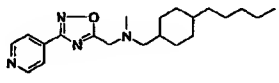
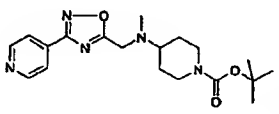
**Example 117:** Methyl-(4-pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine

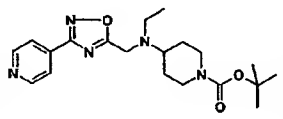
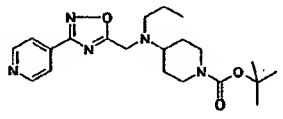
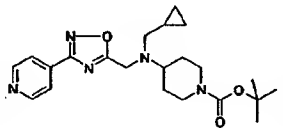
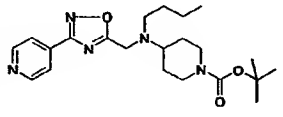
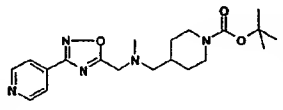
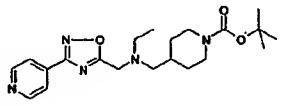
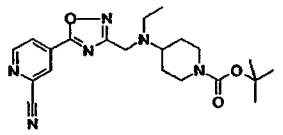


A solution of (4-pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine (**Example 112**, 30.9mg, 94μmol) in dichloroethane (1.3ml) at rt was treated with formaldehyde (8.4ml of a 37% aqueous solution, 103μmol) and sodium triacetoxyborohydride (28mg, 132μmol). After stirring for 48h, the solvent was removed and 2M aqueous sodium hydroxide (1ml) added. The mixture was extracted into EtOAc (25ml) which was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (IH-EtOAc 7:3) to afford the title compound: RT = 3.37min; *m/z* ($ES^+$) = 343.2 $[M+H]^+$.

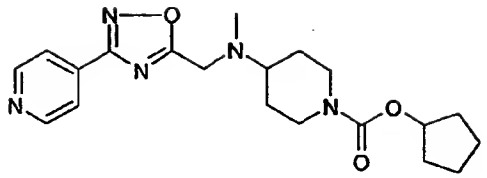
The amines in Table 12 were synthesized in a manner similar to that described in **Example 117**.

**Table 12**

| Ex | Structure | Name | RT (min) | *m/z* ($ES^+$) |
|---|---|---|---|---|
| 118 |  | Methyl-(4-pentylcyclohexylmethyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine | 4.05 | 357.2 $[M+H]^+$ |
| 119 |  | 4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 2.82 | 374.2 $[M+H]^+$ |

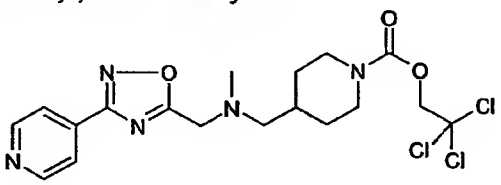
| | | | | |
|---|---|---|---|---|
| **120** |  | 4-[Ethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 3.01 | 388.2 $[M+H]^+$ |
| **121** |  | 4-[Propyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 3.39 | 402.2 $[M+H]^+$ |
| **122** |  | 4-[Cyclopropylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 3.17 | 414.1 $[M+H]^+$ |
| **123** |  | 4-[Butyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester | 3.45 | 416.1 $[M+H]^+$ |
| **124** |  | 4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester | 3.12 | 388.2 $[M+H]^+$ |
| **125** |  | 4-{[Ethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid *tert*-butyl ester | 3.22 | 402.2 $[M+H]^+$ |
| **126** |  | 4-{[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethyl]ethylamino}-piperidine-1-carboxylic acid *tert*-butyl ester | 2.77 | 413.2 $[M+H]^+$ |

**Example 127:** 4-[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid cyclopentyl ester



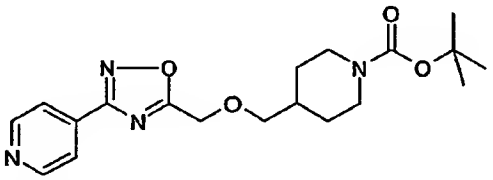
The *tert*-butoxycarbonyl group of 4-[methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester (**Example 119**) was removed using the procedure described in **Example 51** to afford methylpiperidin-4-yl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine: RT = 0.65min; *m/z* ($ES^+$) = 274.0 $[M+H]^+$. Derivatisation of methylpiperidin-4-yl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine with cyclopentylchloroformate, using the procedure described for **Example 52**, afforded the title compound: RT = 3.02min; *m/z* ($ES^+$) = 386.0 $[M+H]^+$.

**Example 128**: 4-{[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}-piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester



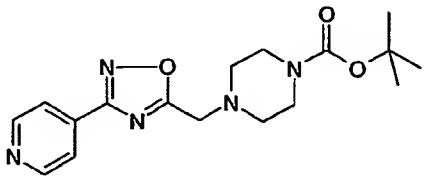
The *tert*-butoxycarbonyl group of 4-{[methyl(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester (**Example 124**) was removed using the procedure described in **Example 51** to afford methylpiperidin-4-ylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine: RT = 0.75min; *m/z* ($ES^+$) = 288.0 $[M+H]^+$. Derivatisation of methylpiperidin-4-ylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine with 2,2,2-trichloroethylchloroformate, using the procedure described for **Example 52**, afforded the title compound: RT = 3.51min; *m/z* ($ES^+$) = 461.9 $[M+H]^+$.

**Example 129**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxymethyl)piperidine-1-carboxylic acid tert-butyl ester



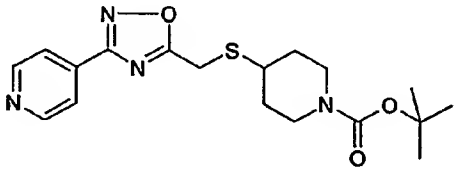
Sodium hydride (19.5mg, 0.49mmol) was added to a solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol (**Preparation 11**, 86mg, 0.49mmol) in anhydrous THF (3ml). After stirring at rt for 5min, 15-crown-5 (97µl, 0.49mmol) was added followed by 4-methanesulfonyloxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (143mg, 0.487mmol). The reaction mixture was heated in a microwave oven (750W) at 100°C for 15min, cooled and the solvent evaporated. The residue was taken up in $CH_2Cl_2$ (100ml), washed with water (10ml), dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.67min; *m/z* ($ES^+$) = 375.2 $[M+H]^+$.

**Example 130**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperazine-1-carboxylic acid *tert*-butyl ester



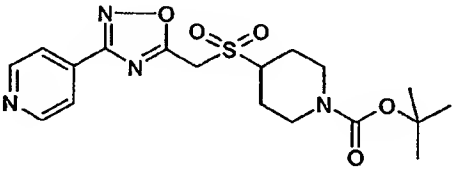
Methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester (**Preparation 12**, 56mg, 0.22mmol) and potassium carbonate (30mg, 0.22mmol) were added to a solution of piperazine-1-carboxylic acid *tert*-butyl ester (37mg, 0.2mmol) in acetonitrile (4ml). The stirred mixture was heated under reflux for 18h, the solvent removed and the residue dissolved in EtOAc-water (90:10, 50ml). The organic phase was separated, washed with brine, dried ($MgSO_4$) and the solvent removed to give a residue which was purified by flash chromatography (IH-EtOAc, 4:1), affording the title compound: RT = 3.26min; *m/z* ($ES^+$) = 346.1 $[M+H]^+$.

**Example 131**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)piperidine-1-carboxylic acid *tert*-butyl ester



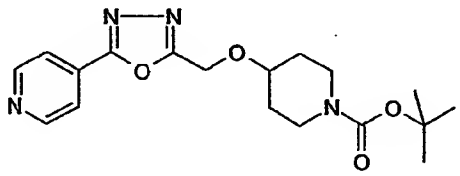
*t*-BuOK (92mg, 823μmol) and methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester (**Preparation 12**, 150mg, 588μmol) were added to a stirred solution of 4-mercaptopiperidine-1-carboxylic acid *tert*-butyl ester (191mg, 881μmol) in anhydrous THF (10ml). After 100min, the reaction mixture was diluted with $Et_2O$, before being washed with $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, then the residue was purified by column chromatography (IH–EtOAc, 3:2) to afford the title compound: RT = 3.77min; *m/z* ($ES^+$) = 377.2 $[M+H]^+$.

**Example 132**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethanesulfonyl)piperidine-1-carboxylic acid *tert*-butyl ester



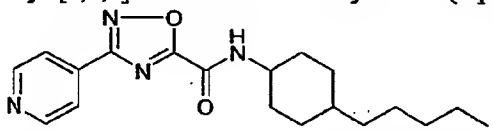
*m*CPBA (111mg of 65% pure, 418μmol) was added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 131**, 105mg, 279μmol) in $CH_2Cl_2$ (7ml). After 110min, the reaction was quenched with saturated aqueous $Na_2CO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Column chromatographic purification (4:1 EtOAc–IH) afforded the title compound: RT = 3.40min; *m/z* ($ES^+$) = 353.1 $[M-t\text{-Bu}+2H]^+$.

**Example 133**: 4-(5-Pyridin-4-yl-[1,3,4]oxadiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



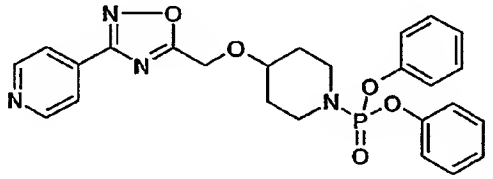
Triethylamine (149µl, 1.06mmol was added to stirred solution of 4-{2-oxo-2-[*N'*-(pyridine-4-carbonyl)hydrazino]ethoxy}piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 16**, 200mg, 0.53mmol) and 2-chloro-1,3-dimethyl-2-imidazolinium hexafluorophosphate (147mg, 0.53mmol) in $CH_2Cl_2$ (10ml). After 18h at rt, the solvent was reduced to a small volume and this mixture purified by flash chromatography (EtOAc), affording the title compound: RT = 3.42min; *m/z* ($ES^+$) = 361.1 $[M+H]^+$.

**Example 134**: 3-Pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid (4-pentylcyclohexyl)amide



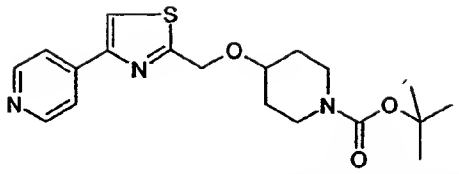
A solution of 3-pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester (50.5mg, 0.23mmol) and 4-pentylcyclohexylamine (39mg, 0.23mmol) in anhydrous toluene (2ml) was treated with trimethylaluminium (345µl of a 2M solution in hexanes, 0.69mmol). After stirring at rt for 18h, saturated aqueous $NaHCO_3$ (2ml) was added and the mixture diluted with $CH_2Cl_2$ (25ml). The organic phase was separated, washed with brine (5ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography to afford the title compound: RT = 4.14min; *m/z* ($ES^+$) = 343.2 $[M+H]^+$.

**Example 135**: [4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]phosphonic acid diphenyl ester



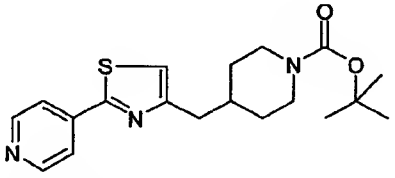
A solution of pyridine (31µl, 0.38mmol) and 4-[5-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (**Preparation 17**, 49mg, 0.19mmol) in $CH_2Cl_2$ (4ml) was treated with phosphorochloridic acid diphenyl ester (103mg, 0.38mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, evaporated and the residue purified by HPLC to afford the title compound: RT = 3.79min, *m/z* ($ES^+$) = 493.1 $[M+H]^+$.

**Example 136**: 4-(4-Pyridin-4-yl-thiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



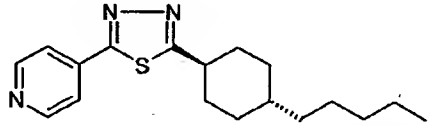
A solution of 2-bromo-1-pyridin-4-yl-ethanone hydrobromide (35mg, 124μmol) and 4-thiocarbamoylmethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 18**, 34mg, 124μmol) in methanol (2ml) was heated at 60°C for 1.5h. The reaction mixture was diluted with EtOAc (60ml), washed with saturated aqueous $NaHCO_3$ (15ml) and brine (15ml) then dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 2.95min, *m/z* ($ES^+$) = 376.1 $[M+H]^+$.

**Example 137**: 4-(2-Pyridin-4-yl-thiazol-4-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester



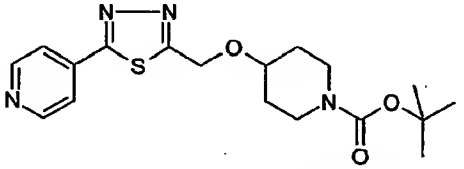
4-(3-Bromo-2-oxopropyl)piperidine-1-carboxylic acid tert-butyl ester was reacted with thioisonicotinamide in a manner similar to that described in **Example 136** to afford the title compound: RT = 3.39min, *m/z* ($ES^+$) = 360.1 $[M+H]^+$.

**Example 138**: *trans*-4-[5-(4-Pentyl-cyclohexyl)-[1,3,4]thiadiazol-2-yl]pyridine



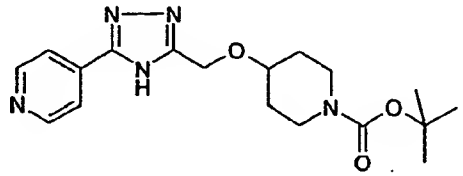
A solution of 4-pentyl-cyclohexanecarboxylic acid *N'*-(pyridine-4-carbonyl)hydrazide (**Preparation 19**, 50mg, 0.158mmol) and Lawesson's reagent (127mg, 0.32mmol) in toluene (2ml) was heated under reflux for 18h. The solvent was evaporated and the residue purified by flash chromatography (IH-EtOAc, 4:1 then EtOAc) to afford the title compound: RT = 5.02min; *m/z* ($ES^+$) = 316.0 $[M+H]^+$.

**Example 139**: 4-(5-Pyridin-4-yl-[1,3,4]thiadiazol-2-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



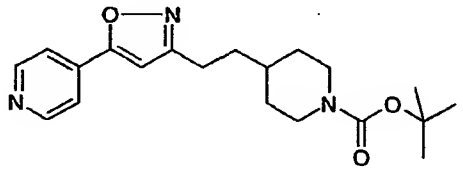
4-{2-Oxo-2-[*N'*-(pyridine-4-carbonyl)hydrazino]ethoxy}piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 16**) was treated with Lawesson's reagent in a similar manner to that described in **Example 138**, affording the title compound: RT = 3.47min, *m/z* ($ES^+$) = 377.1 $[M+H]^+$.

**Example 140:** 4-(5-Pyridin-4-yl-4H-[1,2,4]triazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



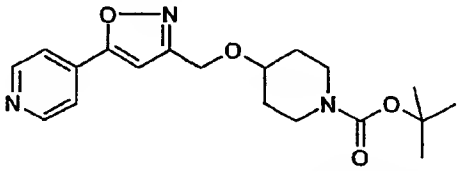
A solution of 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 255mg, 0.952mmol) and triethylamine (138µl, 0.982mmol) in toluene was cooled to 0°C and isobuylchloroformate (127µl, 0.982mmol) added. After stirring at rt for 45min 4-pyridinecarboximidic acid hydrazide (100mg, 0.82mmol) and 3Å powdered molecular sieves (0.82g) were added and the reaction heated under reflux for 18h. On cooling, the mixture was filtered through celite, the filtrate evaporated and the residue dissolved in EtOAc (50ml). After washing with saturated aqueous $Na_2CO_3$ (10ml) and brine (10ml), the solvent was removed and the residue purified by flash chromatography (EtOAc then 5%MeOH in EtOAc) to afford the title compound: RT = 2.81min; *m/z* ($ES^+$) = 360.1 $[M+H]^+$.

**Example 141:** 4-[2-(5-Pyridin-4-yl-isoxazol-3-yl)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester



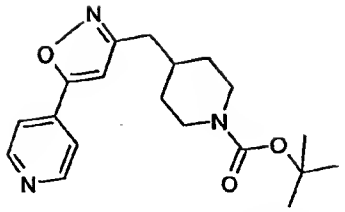
$HONH_2$·HCl (29mg, 418µmol) and $Na_2CO_3$ (29mg, 277µmol) were added to a stirred solution of 4-(3,5-dioxo-5-pyridin-4-ylpentyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 22**, 98mg, 271µmol) in EtOH (0.75ml) and $H_2O$ (0.45ml). The reaction was heated at 70°C (bath) for 4h, then the solvents were removed under reduced pressure. The residue was purified by RP-HPLC to afford the title compound: RT = 3.57min; *m/z* ($ES^+$) = 358.3 $[M+H]^+$.

**Example 142:** 4-(5-Pyridin-4-yl-isoxazol-3-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester



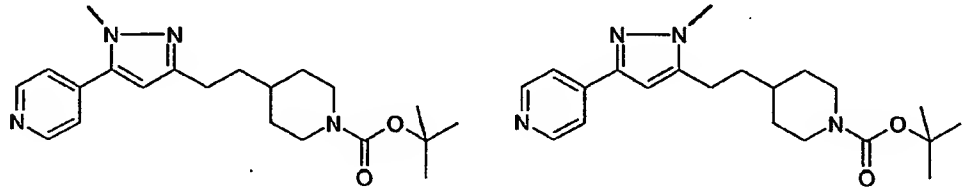
Condensation of $HONH_2$ with 4-(2,4-dioxo-4-pyridin-4-ylbutoxy)piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 23**), as outlined in **Example 141**, afforded the title compound: RT = 3.34min; *m/z* ($ES^+$) = 360.3 $[M+H]^+$.

**Example 143:** 4-(5-Pyridin-4-yl-isoxazol-3-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester



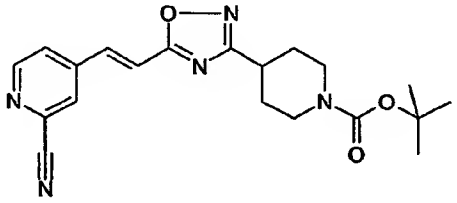
Condensation of $HONH_2$ with 4-(2,4-dioxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid tert-butyl ester (**Preparation 24**), as outlined in **Example 141**, afforded the title compound: RT = 3.47min; *m/z* ($ES^+$) = 344.3 $[M+H]^+$.

**Examples 144 and 145**: 4-[2-(1-Methyl-5-pyridin-4-yl-1H-pyrazol-3-yl)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester and 4-[2-(2-Methyl-5-pyridin-4-yl-2H-pyrazol-3-yl)ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester



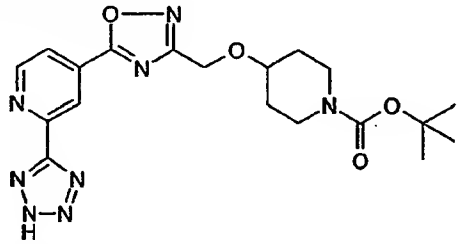
$MeNHNH_2$ (16mg, 348μmol) was added to a stirred solution of 4-(3,5-dioxo-5-pyridin-4-yl-pentyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 22**, 96mg, 268μmol) in EtOH (1ml). The reaction was heated under reflux for 4h, then the solvents were removed under reduced pressure. The residue was purified by RP-HPLC to afford **Example 144**: RT = 3.22min; *m/z* ($ES^+$) = 371.3 $[M+H]^+$; and **Example 145**: RT = 2.99min; *m/z* ($ES^+$) = 371.3 $[M+H]^+$.

**Example 146**: (*E*)-4-{5-[2-(2-Cyanopyridin-4-yl)vinyl]-[1,2,4]oxadiazol-3-yl}piperidine-1-carboxylic acid *tert*-butyl ester



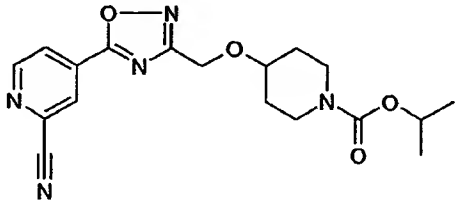
A solution of *m*CPBA (9.4mg of 77% pure, 42μmol) in $CHCl_3$ (0.5ml) was added to a stirred solution of (*E*)-4-[5-(2-pyridin-4-ylvinyl)-[1,2,4]oxadiazol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester (**Example 46**, 15mg, 42μmol) in $CHCl_3$ (1ml) at 0°C. The mixture was stirred at 20°C for 16h, before being treated with more *m*CPBA (2.5mg of 77% pure, 11μmol). After 2h, the reaction was concentrated, then the residue was purified by column chromatography (EtOAc then THF) to yield (*E*)-4-{5-[2-(1-oxypyridin-4-yl)vinyl]-[1,2,4]oxadiazol-3-yl}piperidine-1-carboxylic acid *tert*-butyl ester: *m/z* ($ES^+$) = 373.3 $[M+H]^+$. This *N*-oxide (13mg, 35μmol) was treated with TMS–CN (14μl, 130μmol), $NEt_3$ (10μl, 70μmol), $CH_2Cl_2$ (250μl) and $Me_2NCOCl$ (3μl). After 18h, the solvents were evaporated and the residue purified by column chromatography (IH–EtOAc, 1:1) to afford the title compound: RT = 3.99min; *m/z* ($ES^+$) = 382.3 $[M+H]^+$.

**Example 147**: 4-{5-[2-(2H-Tetrazol-5-yl)pyridin-4-yl]-[1,2,4]oxadiazol-3-ylmethoxy} -piperidine-1-carboxylic acid *tert*-butyl ester



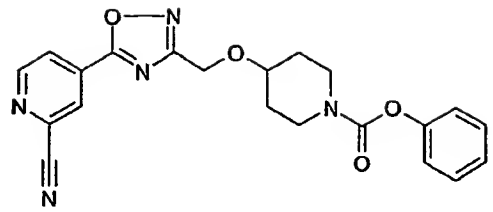
To a stirred solution of 4-[5-(2-cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid *tert*-butyl ester (**Example 42**, 52mg, 0.14mmol) in DMF (3ml) heated to 90°C was added sodium azide (9mg, 0.15mmol) as a suspension in DMF (2ml). After 3h, sodium azide (18mg, 0.29mmol) was added in one portion and the reaction mixture stirred at 90°C for a further 16h. The reaction mixture was allowed to cool to rt then all solvents were removed *in vacuo*. The residue was suspended in EtOAc then filtered through a sinter, washing with EtOAc. The solid was partitioned between EtOAc (20ml) and water (10ml) containing AcOH (5 drops). The layers were separated then the aqueous extracted with EtOAc (3x20ml). The combined organics were washed with brine (20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound which needed no further purification: RT = 3.44min; *m/z* ($ES^+$) = 429.1 $[M+H]^+$.

**Example 148**: 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid isopropyl ester



To a stirred solution of 4-[3-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile (**Preparation 25**, 300mg, 1.1mmol) in DCM (10ml) was added triethylamine (0.3ml, 2.1mmol). The resulting solution was transferred to a stirred solution of isopropylchloroformate (2.1ml of a 1M solution in PhMe, 2.1mmol) in DCM (30ml) and stirring was continued for 30min at rt. The reaction mixture was diluted with EtOAc (30ml) then washed successively with water (50ml), saturated aqueous sodium carbonate (50ml) and brine (50ml). The organics were dried ($MgSO_4$) then adsorbed onto silica gel. Purification via chromatography (EtOAc-I.H, 1:1) afforded the title compound: RT = 3.44min; *m/z* ($ES^+$) = 372.04 $[M+H]^+$.

**Example 149**: 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid phenyl ester



To a stirred solution of 4-[3-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile (**Preparation 25**, 700mg, 2.5mmol) in DCM (30ml) was added triethylamine (0.7ml, 4.9mmol). The resulting solution was transferred to a stirred solution of phenylchloroformate (0.62ml, 4.9mmol) in DCM (30ml) and stirring was continued for 30min at rt. The reaction mixture was diluted with EtOAc (250ml) then washed successively with water (100mL), saturated aqueous sodium carbonate (100ml) and brine (100ml). The organics were dried ($MgSO_4$) then adsorbed onto silica gel. Purification via chromatography (EtOAc-LH, 1:1 to 3:2) afforded the title compound: RT = 3.63min; *m/z* ($ES^+$) = 406.01 $[M+H]^+$.

The biological activity of the compounds of the invention may be tested in the following assay systems:

**Yeast Reporter Assay**

The yeast cell-based reporter assays have previously been described in the literature (e.g. see Miret J. J. et al, 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al, 1999, Bioorg. Med. Chem. Lett., 9:2413-2418; King K. et al, 1990, Science, 250:121-123); WO 99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPA1) has been deleted and replaced with G-protein chimeras constructed using multiple techniques. Additionally, the endogenous yeast alpha-cell GPCR, Ste3 has been deleted to allow for a homologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fus1. By placing β-galactosidase (LacZ) under the control of the Fus1 promoter (Fus1p), a system has been developed whereby receptor activation leads to an enzymatic read-out.

Yeast cells were transformed by an adaptation of the lithium acetate method described by Agatep et al, (Agatep, R. et al, 1998, Transformation of Saccharomyces cerevisiae by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier). Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10μg), 2μg of each of two Fus1p-LacZ reporter plasmids (one with URA selection marker and one with TRP), 2μg of GPR116 (human or mouse receptor) in yeast expression vector (2μg origin of replication) and a lithium acetate/ polyethylene glycol/ TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60min. The yeast cells were then heat-shocked at 42°C for 15min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-

LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for β-galactosidase, yeast cells carrying the human or mouse GPR116 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells were still dividing and had not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90µl of yeast cells are added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the β-galactosidase was added to each well. In these experiments, Fluorescein di (β-D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20µl per well of 500µM FDG/2.5% Triton X100 was added (the detergent was necessary to render the cells permeable). After incubation of the cells with the substrate for 60min, 20µl per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without compound).

**cAMP Assay**

A stable cell line expressing recombinant human GPR116 was established and this cell line was used to investigate the effect of compounds of the invention on intracellular levels of cyclic AMP (cAMP). The cells monolayers were washed with phosphate buffered saline and stimulated at 37°C for 30min with various concentrations of compound in stimulation buffer plus 1% DMSO. Cells were then lysed and cAMP content determined using the Perkin Elmer AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions were as described in the manufacturer's protocol. Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level and generally had an $EC_{50}$ of <10µM.

**In vivo feeding study**

The effect of compounds of the invention on body weight and food and water intake was examined in freely-feeding male Sprague-Dawley rats maintained on reverse-phase lighting. Test compounds and reference compounds were dosed by appropriate routes of administration (e.g. intraperitoneally or orally) and measurements made over the following 24 h. Rats were individually housed in polypropylene cages with metal grid floors at a temperature of 21±4°C and 55±20% humidity. Polypropylene trays with cage pads were placed beneath each cage to detect any food spillage. Animals were maintained on a reverse phase light-dark cycle (lights off for 8 h from 09.30-17.30 h) during which time the room was illuminated by red light. Animals had free access to a standard powdered rat diet and tap water during a two week acclimatization period. The diet was contained in glass feeding jars with aluminum lids. Each lid had a 3-4 cm hole in it to allow access to the food. Animals, feeding jars and water bottles were weighed (to the nearest 0.1 g) at the onset of the dark period. The feeding jars and water bottles were subsequently measured 1, 2, 4, 6 and 24 h after animals were dosed with a

compound of the invention and any significant differences between the treatment groups at baseline compared to vehicle-treated controls.

Selected compounds of the invention showed a statistically significant hyperphagic effect at one or more time points at a dose of < 100mg/kg.

WHAT IS CLAIMED IS:

1. A compound of formula (I), pharmaceutically acceptable salt thereof:

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S, optionally substituted by $C_{1-4}$ alkyl;

A is -CH=CH- or $(CH_2)_n$;

B is -CH=CH- or $(CH_2)_n$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$, C(O) or $C(O)NR^{12}$;

n is independently 0, 1, 2 or 3;

m is independently 0, 1 or 2;

$R^1$ is 3- or 4-pyridyl, 4- or 5-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

$R^2$ is 4- to 7-membered cycloalkyl substituted by $R^3$, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$, $P(O)(OR^{11})_2$ or a 5- or 6-membered nitrogen containing heteroaryl group;

$R^3$ is $C_{3-8}$ alkyl, $C_{3-8}$ alkenyl or $C_{3-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^5$ is hydrogen, $C(O)R^7$, $S(O)_2R^8$, $C_{3-7}$ cycloalkyl or $C_{1-4}$ alkyl optionally substituted by $OR^6$, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-2}$ alkyl, $C_{1-2}$ fluoroalkyl, $OR^6$, CN, $N(R^6)_2$ and $NO_2$;

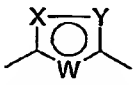
$R^6$ are independently hydrogen $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^7$ is hydrogen, $C_{1-4}$ alkyl, $OR^6$, $N(R^6)_2$, aryl or heteroaryl;

$R^8$ is $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, aryl or heteroaryl;
$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl;
$R^{10}$ is hydrogen or $C_{1-4}$ alkyl;
$R^{11}$ is phenyl; and
$R^{12}$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-7}$ cycloalkyl;
provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid $^t$butyl ester;
c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;
d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or
e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein V represents a 5-membered heteroaryl ring containing up to three heteroatoms selected from O, N and S of the formula:




wherein W, X and Y represent the positions of the heteroatom(s) or otherwise represent CH.

3. A compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein two of W, X and Y are N, and the other is O.

4. A compound according to claim 2 or 3, or a pharmaceutically acceptable salt thereof, wherein W is N.

5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the n groups of A and B do not both represent 0.

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein in A, n is 0, 1 or 2.

7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein in B, n is 2 or 3.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is 4-pyridyl optionally substituted by 1 or 2 halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, 4- to 7-membered heterocyclyl or 5- or 6-membered heteroaryl groups.

9. A compound according to claim 8, or a pharmaceutically acceptable salt thereof; wherein $R^1$ is 4-pyridyl optionally substituted by halo, $C_{1-4}$ alkyl $C_{1-4}$ alkoxy or CN.

10. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is a 4- to 7-membered cycloalkyl substituted by $R^3$, or 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by $C(O)OR^4$.

11. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^3$ is $C_{3-8}$ alkyl which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl.

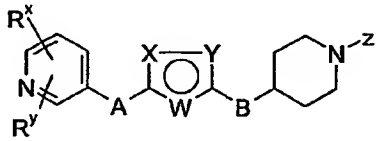
12. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, 5- to 6-membered heteroaryl containing one or two nitrogen atoms, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl or $C_{1-4}$ alkylaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$ and $CO_2C_{1-4}$ alkyl.

13. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is $C_{3-6}$ alkyl optionally substituted with up to 5 fluoro or chloro atoms, and which may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is $C_{1-4}$ alkyl.

15. A compound of formula (I) as defined in any one of Examples 1, 3 to 8, 10 to 13, 16 to 50, or 52 to 149, or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 having the formula (Id), or a pharmaceutically acceptable salt thereof:



(Id)

where two of W, X and Y are N, and the other is O;

A is -CH=CH- or $(CH_2)_n$;

B is -CH=CH- or $(CH_2)_n$, where one of the $CH_2$ groups may be replaced by O, $NR^5$, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3, provided that not both n are 0;

m is independently 0, 1 or 2;

$R^x$ and $R^y$ are independently selected from hydrogen, halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group and a 5- or 6-membered heteroaryl group;

Z is $C(O)OR^4$, $C(O)R^3$, $S(O)_2R^3$, $C(O)NHR^4$ or a 5- or 6-membered nitrogen containing heteroaryl group;

$R^3$ is $C_{3-8}$ alkyl, $C_{3-8}$ alkenyl or $C_{3-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

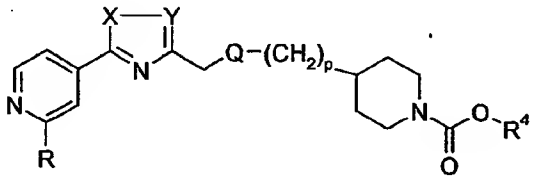
$R^5$ is hydrogen or $C_{1-4}$ alkyl;

$R^6$ are independently hydrogen, or $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl; and

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl.

17. A compound according to claim 1 having the formula (Ie), or a pharmaceutically acceptable salt thereof:



(Ie)

wherein one of X and Y is N, and the other is O;

Q is O, $NR^5$ or $CH_2$;

R is hydrogen, halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, $OR^6$, CN, $NO_2$, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

$R^4$ is $C_{2-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and contain a $CH_2$ group that may be replaced by O, or $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{1-4}$ alkyl$C_{3-7}$ cycloalkyl, $C_{1-4}$ alkylaryl, $C_{1-4}$ alkylheterocyclyl or $C_{1-4}$ alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^6$, CN, $CO_2C_{1-4}$ alkyl, $N(R^6)_2$ and $NO_2$;

$R^5$ is $C_{1-4}$ alkyl;

$R^6$ are independently hydrogen, or $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^9$, CN, $SO_2CH_3$, $N(R^{10})_2$ and $NO_2$; or a group $N(R^{10})_2$ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and $NR^{10}$;

$R^9$ is hydrogen, $C_{1-2}$ alkyl or $C_{1-2}$ fluoroalkyl;

$R^{10}$ is hydrogen or $C_{1-4}$ alkyl; and

p is 0 or 1.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17, including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

19. A method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

20. A method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

21. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

22. A method for the treatment of diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/050046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/04 C07D413/06 C07D413/12 A61K31/4245

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 98/17652 A (BOEHRINGER INGELHEIM PHARMA KG; BOEHRINGER INGELHEIM INTERNATIONAL GMB) 30 April 1998 (1998-04-30) page 66, line 17 - page 67, line 1 claim 1 | 1-22 |
| X | WO 01/12627 A (NPS PHARMACEUTICALS, INC; VAN WAGENEN, BRADFORD, C; STORMANN, THOMAS,) 22 February 2001 (2001-02-22) page 5, lines 19-22 figure 1 claim 1 | 1-22 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 April 2005 | 28/04/2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Samsam Bakhtiary, M |

Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB2004/050046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/068417 A (NPS PHARMACEUTICALS, INC; SLASSI, ABDELMALIK; VAN WAGENEN, BRADFORD; S) 6 September 2002 (2002-09-06)<br>page 33; compounds B66,B69,B71,B72,B73,B74<br>page 35; compound B111<br>page 36; compound B123<br>page 41; compounds B226,B182 | 1-22 |
| X | US 6 239 160 B1 (TIEBES JOERG ET AL)<br>29 May 2001 (2001-05-29)<br>table 1; compounds<br>156,337,370,388,394,433,442,481,495,542<br>table 2; compound 738<br>table 4; compounds 1127,1168 | 1-22 |
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